A-20.
2.9.88

VOLUME 61 • NUMBER 1 • JULY 1988

British Journal of Anaesthesia

Editor: GRAHAM SMIT

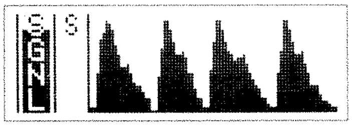
Voices of Experience.

Why Pulse Oximetry Isn't Pulse Oximetry Without a Waveform.

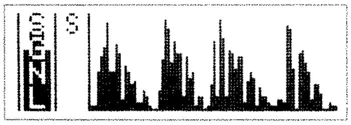
"...interference, such as from a pulsatile light source, may cause erroneous SaO_2 readings. An oximeter with a pulse waveform, rather than just bouncing dots, may be better able to detect interference because it can indicate a discrepancy from the norm.

"A well-designed oximeter should be able to detect power line frequency, compensate for background light flicker such as with fluorescent lamps, and display a true pulse waveform rather than bouncing dots."

Jeffrey B. Gross, M.D.
Associate Professor of Anesthesia
University of Pennsylvania,
Philadelphia, Pennsylvania



In the presence of a clean, physiological signal, the waveform is smooth, uniform and pulsatile in shape. The higher the signal strength indicator, the stronger the signal.



In the presence of interference, the waveform shows a noisy plethysmograph.

P25757
1

"In several of our studies of hypoxemia where it was important that the researchers and clinicians be blinded from the results, we found the waveform to be useful to distinguish real data from artifact."

Daniel B. Raemer, Ph.D.
Assistant Professor of
Anesthesia (Bioengineering)
Brigham and Women's Hospital
and Harvard Medical School
Boston, Massachusetts

"Observing the waveform is a vital aid to instantly rejecting artifact and is useful in providing extra data about the patient's cardiovascular system."

Richard Morris
M.B.B.S., F.F.A.R.C.S.
Staff Specialist
Department of Anaesthesia
and Intensive Care
Prince Henry Hospital
Little Bay, New South Wales
Australia

"Because the SaO_2 produced by the pulse oximeter is based on pulsatile absorbance of light, the pulsatile waveform is the essential quality control indicator."

William T. Cecil, R.R.T.
Coordinator
Respiratory Care Services
St. Luke's Hospital
Kansas City, Missouri

"I feel secure that the information I am getting is based on a good pulse. I can trust the reading."

Gayle Miller, R.N.
Unit Administrator
Post-Anesthesia Care Unit
University Hospital
University of Colorado
Health Sciences Center
Denver, Colorado

"We would not consider purchase of a saturation monitor that did not have a waveform."

Anneke Meursing, M.D.
Anesthesia Department
Sophia's Children's Hospital
Rotterdam, Netherlands

"The waveform provides troubleshooting at a glance."

Jeffrey A. Neilsen, C.R.N.A.
Staff Nurse Anesthetist
Christian Hospital
Northeast-Northwest
St. Louis, Missouri

The Ohmeda Biox 3700 Pulse Oximeter.

All oximeters can be affected by external light sources.[1-5] On a non-waveform oximeter, optical interference can go undetected and lead to erroneous SaO_2 readings. On a waveform oximeter, however, the plethysmograph is a representation of the detected signal that informs you of optical interference, as well as interference from motion.

Our waveform keeps you informed. It's your best insurance against undetected interference.

The result is more reliable SaO_2 readings.

And that's why without the waveform, pulse oximetry isn't pulse oximetry.

The Ohmeda Biox 3700. The world's first waveform pulse oximeter.

Everyone's talking about it.

---

[1] Costarino AT, Davis DA, Keon TP: Falsely normal saturation reading with the pulse oximeter. *Anesthesiology* 67:830–831, 1987. [2] Hanowell L, Eisele JH Jr, Downs D: Ambient light affects pulse oximeters, Correspondence. *Anesthesiology* 67:864–865, 1987. [3] Swedlow DB, Running V, Feaster SJ: Correspondence. *Anesthesiology* 67:865, 1987. [4] Block FE Jr: Interference in a Pulse Oximeter from a Fiberoptic Light Source. *Journal of Clinical Monitoring*, July 1987, pp 210–211. [5] Brooks T, Paulus D, Winkle W: Infrared Heat Lamps Interfere with Pulse Oximeters. *Anesthesiology* 61:630, 1984

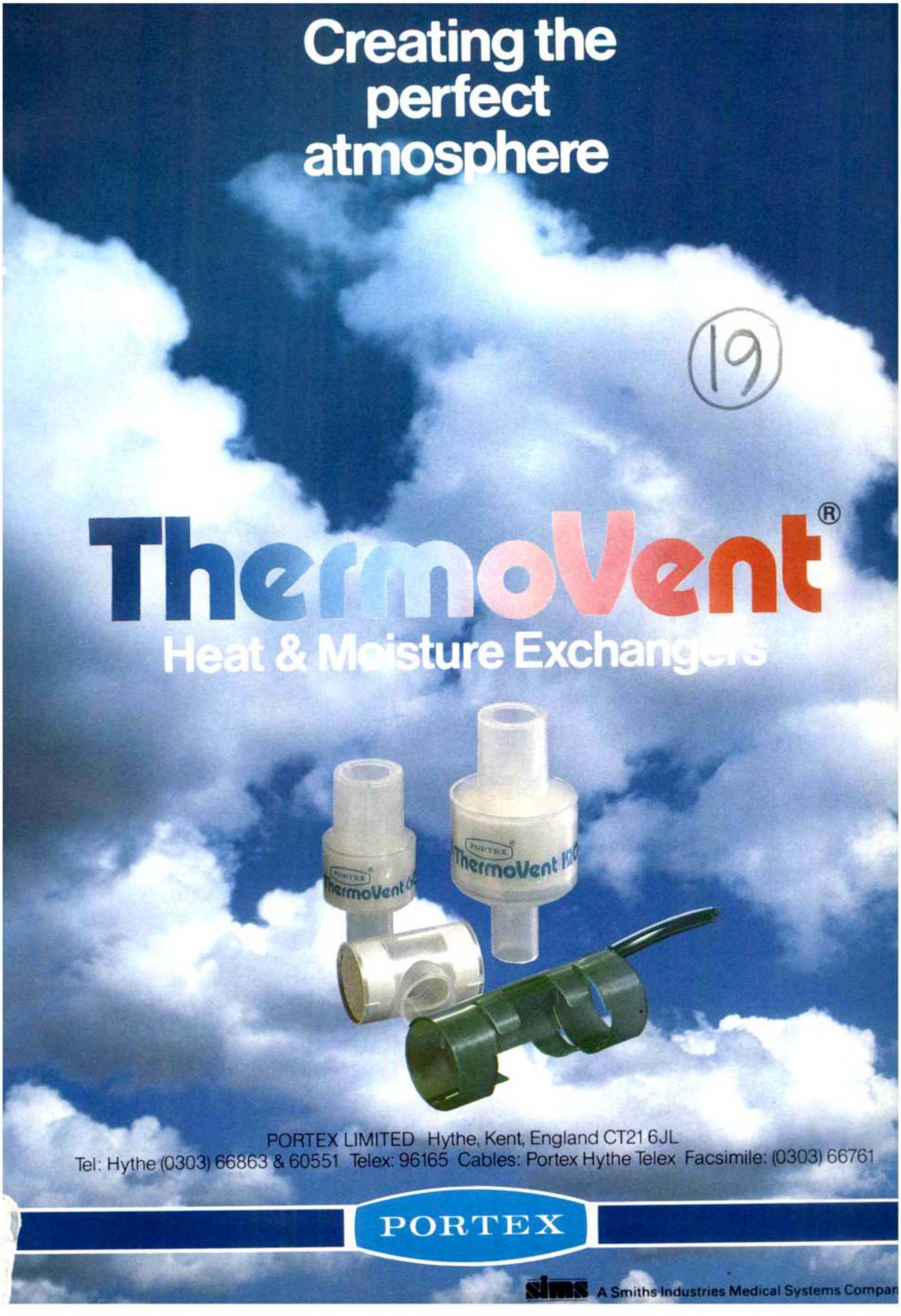
Ohmeda

Ohmeda
Elizabeth Way
Harlow, Essex CM19 5AB
United Kingdom Tel: 279 29692

Ohmeda
1315 West Century Drive
Louisville CO 80027 USA
Tel 303 666 7001 Telex 296 445 BTI UR

BOC Health Care

©1987 The BOC Group



PORTEX LIMITED Hythe, Kent, England CT21 6JL
Tel: Hythe (0303) 66863 & 60551 Telex: 96165 Cables: Portex Hythe Telex Facsimile: (0303) 66761

PORTEX

sims A Smiths Industries Medical Systems Compan

GUIDE TO CONTRIBUTORS

The purpose of the *British Journal of Anaesthesia* is the publication of original work in all branches of anaesthesia, including the application of basic sciences. One issue each year deals mainly with material of postgraduate educational value.

PAPERS

Papers submitted must not have been published in whole or in part in any other journal, and are subject to editorial revision. It is a condition of acceptance for publication that copyright becomes vested in the journal and permission to republish must be obtained from the Editor.

Papers based on clinical investigation should conform to ethical standards as set out in the Declaration of Helsinki. In the case of animal studies it is the responsibility of the author to satisfy the Board that no unnecessary suffering has been inflicted.

LEGAL CONSIDERATIONS

Authors should avoid the use of names, initials and hospital numbers which might lead to recognition of a patient. A patient must not be recognizable in photographs unless written consent of the subject has been obtained. A table or illustration that has been published elsewhere should be accompanied by a statement that permission for reproduction has been obtained from the author and publishers.

PREPARATION OF MANUSCRIPT

Three copies of each manuscript should be submitted and should indicate the title of the paper, the name(s), qualifications and full address(es) of the author(s), and be in letter quality heavy type (not dot matrix), double-spaced on one side only of the paper, with a wide margin. Contributors should retain a copy in order to check proofs and in case of loss.

Manuscripts should be accompanied by a formal letter of request for publication which should be signed by all of the authors.

Papers in recent issues of the *British Journal of Anaesthesia* should be consulted for general and detailed presentation. They are most often subdivided into:

Title page
Summary
Introduction (not headed)
Methods
Results
Discussion
Acknowledgements
List of references
Tables
Illustrations

Title page

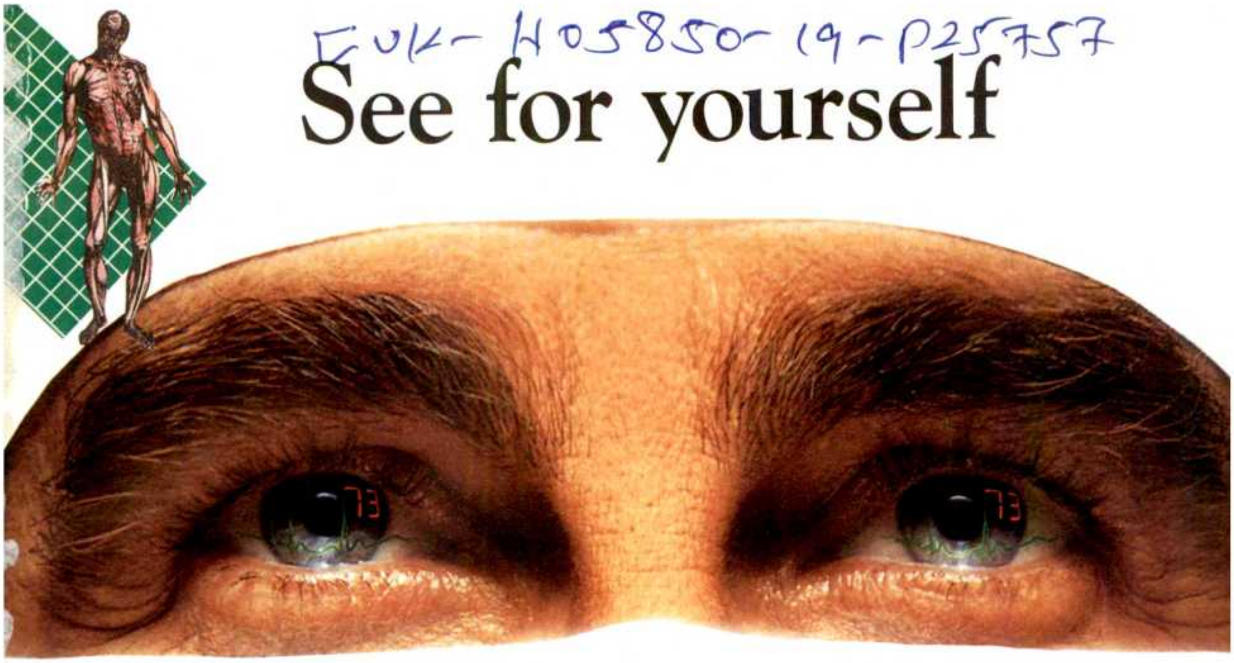
There should be a separate title page, including the name(s), degrees and address(es) of author(s). It should be made clear which address relates to which author. Authors' present addresses differing from those at which the work was carried out, or special instructions concerning the address for correspondence, should be given as a footnote on the title page and referenced at the appropriate place in the author list by superscript symbols. If the address to which proofs should be sent is not that of the first-mentioned author, clear instructions should be given in a covering note and not on the title page. The title page should be paginated as page 1 of the paper.

A short running title containing not more than 50 characters and spaces, and three to five key words or phrases (for indexing) should be included.

Summary

The summary will be printed at the beginning of the paper. It should be on a separate sheet, in the form of a single paragraph which gives a succinct account of the problem, the methods, EUK-H05850-19-P25757

See for yourself



NORCURON®

vecuronium bromide

Muscle relaxation, pure and simple

- Highly specific for the neuromuscular junction
- Flexible and versatile in its application
- Minimal histamine release

NORCURON

ORGANON TEKNIKA

Further information is available from:
Organon Teknika Limited
Cambridge Science Park, Milton Road,
Cambridge CB4 4FL

Prescribing Information: Norcuron vials of 10mg vecuronium bromide with 5ml ampoule water for injection. **Uses:** Non-depolarising neuromuscular blocking agent of short to medium duration. **Dosage:** Intravenous Initial 80-100 micrograms/kg. Incremental 30-50 micrograms/kg. Infusion 50-80 micrograms/kg/hr. **Contraindications:** None known. Since there is no experience with the use of Norcuron in pregnant women, it cannot be recommended during pregnancy. Clinical studies show that Norcuron can be used in childbirth by Caesarian section without effect on the newly born child. **Precautions and warnings:** In renal insufficiency a slight prolongation of neuromuscular block can be expected. Use very small doses, and extreme caution in myasthenia gravis or myasthenic syndrome unless prolonged post-operative respiratory assistance is intended. Dose carefully in myopathy, severe obesity, electrolyte disturbances, altered pH and after poliomyelitis or dehydration. Neuromuscular blockade can be reversed with adequate doses of neostigmine together with atropine. **Interaction:** It is dangerous to give depolarising drugs (e.g. suxamethonium chloride) following a non-depolarising drug (e.g. Norcuron). Alkylating drugs (nitrogen mustards) may be a hazard in anaesthesia involving muscle relaxants. Anaesthetics, other drugs and the condition of the patient, may affect the magnitude and or duration of action of **Norcuron** – see Data Sheet. **Side-effects:** There has been a single, unconfirmed report of histamine release occurring in a patient treated with a combination of drugs, one of which was Norcuron. There have been no other reported adverse reactions. **Overdosage:** Use standard reversal agents, e.g. neostigmine or pyridostigmine. **Packs:** 20 vials 10mg **Norcuron,** 20 ampoules 5ml water for injection. PL: 3524/0013.

results and conclusions, and normally should be of 50–150 words. It may be used as it stands by abstracting journals.

Introduction

The introduction should give a concise account of the background of the problem and the object of the investigation. Previous work should be quoted only if it has a direct bearing on the present problem.

Methods

Methods must be described in sufficient detail to allow the investigation to be interpreted and repeated by the reader. Any modification of previously published methods should be described and the reference given. If the methods are commonly used, only a reference to the original source is required.

Drugs

When a drug is first mentioned it should be given the generic or official name, followed in parentheses by the chemical formula only if the structure is not well known, and by the capitalized proprietary name.

Results

Description of results, while concise, should permit repetition of the investigation by others. Data should not be repeated unnecessarily in text, tables and figures, and unwarranted numbers of digits should be avoided. Significance should be given as values of probability. The desired positions of tables and figures may be indicated by written instructions enclosed within lines and brackets, for example:

(TABLE III near here)

Discussion

The discussion should not merely recapitulate the results, but should present their interpretation against the background of existing knowledge. It should include a statement of any assumptions on which conclusions are based.

Acknowledgements

Acknowledgements will be printed in small type. They should be brief, and should include reference to sources of support and sources of drugs not freely available commercially.

References

There should be a table of references at the conclusion of the paper, commencing on a new sheet.

References must be numbered consecutively in the order in which they are first mentioned in the text, with the exception of review articles, when references should be arranged alphabetically.

References in text, tables and legends should be identified by arabic numbers appearing in the text in square brackets.

Use the style of references adopted by the U.S. National Library of Medicine and used in *Index Medicus*. The titles of journals must be given in full.

The names and initials of *all* authors should be listed.

Text references to "unpublished observations" or "personal communications" should not be included in the final list of references. Authors are responsible for verifying that the wording of references to unpublished work is approved by the persons concerned. Papers which have been submitted *and accepted* for publication should be included in the list, the phrase "in press" replacing volume and page number. Information from manuscripts submitted but not yet accepted should be cited in the text as unpublished observations.

Examples of correct forms of references:

Journals (list *all* authors):

Brown B R jr, Gandolphi A J. Adverse effects of volatile anaesthetics. *British Journal of Anaesthesia* 1987; 59: 14–23.

Chapter in a Book:

Hull C J. Opioid infusions for the management of post-operative pain. In: Smith G, Covino B G, eds. *Acute Pain*. London: Butterworths, 1985: 155–179.

Monographs:

Moore, D C. *Regional Block*, 4th edn. Springfield, Illinoi Charles C Thomas, 1979.

Restrict references to those that have dire bearing on the work described and cite or references to books and articles published *Index Medicus* journals.

It is essential that authors verify the con and detail of references which they list agains original articles, as this responsibility cann accepted by either Editors or publishers.

BIODATA

RECALL

A Unique Computerized Anaesthetics Record Keeping System.

RECALL is a completely new system for automated anaesthetics record keeping. It provides crisp, accurate and comprehensive printed records and a host of features which eliminate the problems of manual methods.

During the operation RECALL gathers data from all your patient monitors whatever their make or type. A full colour display of vital signs allows trends to be assessed at a glance.

In addition, a range of user-definable menus allows intra-operative details to be entered with a few keystrokes.

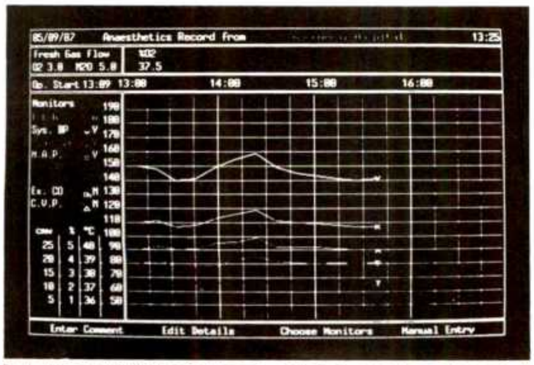
Comments and drug administrations are timed automatically.

At the end of the operation RECALL prints a full anaesthetics record, and all data are stored in a secure computer database from where they can be retrieved in seconds.

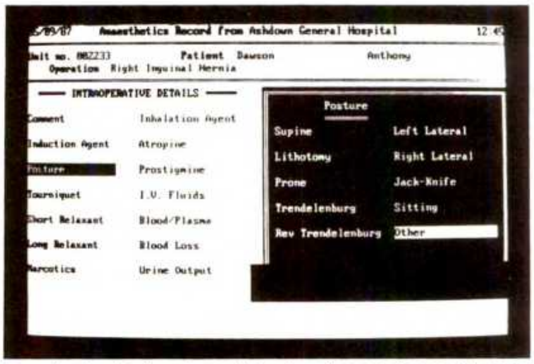
RECALL provides:

- Menu-driven software
- Freedom to use any combination of patient monitors
- Real-time record keeping
- Complete patient database management

Sales literature and further information from:
Biodata Ltd., 10 Stocks St., Manchester M8 8QG, U.K
Tel: 061-834 6688 Telex: 665608 BIODAT G



Real-time trended display of vital signs – each measure is integrated on a single screen. Comments can be typed in during the operation for later review.



5/09/87 Anaesthetics Record from Ashdown General Hospital 12:45

nit no. 002233 Patient Dawson Anthony

Operation Right Inguinal Hernia

Intra-operative details – all anaesthetics procedures can be recorded. Entries can be typed in when not listed in the menus.

Tables

All tables should be on separate sheets and be capable, with their captions, of interpretation without reference to the text. They should be numbered consecutively with roman numerals. Units in which results are expressed should be given in brackets at the top of each column, and not repeated on each line of the table. Ditto signs are not used. Footnotes are not used.

Illustrations

Photographs should be unmounted glossy prints, and should be protected adequately for mailing. Surfaces should not be marred with clips, pins or by heavy writing on the back. Drawings, charts and graphs should be in black india ink on white paper and, if in sets, should be presented at a uniform magnification. Illustrations should be clearly numbered on the back, preferably in soft pencil, with reference to the text, and using arabic numerals. They should be accompanied on a separate sheet by a suitable legend. Lettering should be professional-looking, uniform, preferably in a common typeface, large enough to read at a reduced size, and in proportion to the illustrated material. Lines in the original must also be thick enough to allow for reduction. Magnifications, especially in photomicrographs, should be indicated by a scale on the photograph itself, in order to remain appropriate after reduction. Symbols which are to appear in the legend should be chosen from the following available types:

● ○ ■ □ ▼ ▽ ▲ △ ◆ ◇ × +

The name of the author and title of the paper should also be written in soft pencil on the back of the illustrations.

It is emphasized that care taken in the original preparation of figures will obviate the time-consuming and expensive necessity of their revision.

General information

Instructions to the printer. Words to be printed in lower-case italics should be indicated by one underline. Two underlines indicate small capitals, three indicate large capitals and four, italic capitals. A wavy underline indicates a word to be printed in bold type.

Headings in the text. Six possible grades are available, and may be indicated by the following letters of identification:

A	PART I	(capitals)
B	RESULTS	(small capitals)
C	Blood-Gas Analysis	(l.c. roman)
D	*The Action of Drugs*	(italics, centre)
E	*Lung function studies*	(italics, full out)
F	*Volume.* Large volumes...	(italics, indent)

Symbols and Abbreviations. In accordance with Editorial adoption of SI Units, abbreviations and symbols should follow the conventions described in the booklet *Units, Symbols and Abbreviations. A Guide for Biological and Medical Editors and Authors* (ed. G. Ellis), published by and available from The Royal Society of Medicine, 1 Wimpole Street, London, W1M 8AE. Words for which abbreviations are not included should be written in full at first mention in the summary and again in the text and followed by the abbreviation in brackets. This will usually be in the form of large capitals without separating points.

Spelling, etc. British spelling should be used with "z" rather than "s" spelling in, e.g. organize, organization.

CORRESPONDENCE

It is proposed that a proportion of the Journal be devoted to correspondence each month. Every effort will be made to ensure that correspondence arising from papers in a recent issue is published without delay, and for this reason, relevant correspondence will be given priority over that pertaining to original research. Authors of correspondence concerning original work will receive proofs at the Editor's discretion.

PROOFS

These should be corrected and returned to the technical editor *within 48 hours of receipt*. Overseas contributors should return their proofs by airmail.

REPRINTS

Twenty-five reprints of articles will be dispatched to the authors after publication. Further reprints can be supplied if application is made on the order form attached to the proofs. The order form should be returned with the proofs.

"I would have everie man write what he knowes and no more."—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 61, No. 1 JULY 1988

EDITORIAL

ANAESTHESIA AND MYOCARDIAL ISCHAEMIA

Ischaemic heart disease (IHD) is the most important health care problem affecting adults in the working population of the Western World. For males in the age range 45–54 yr, almost 40 % of all deaths in England and Wales result from IHD, whilst in females the prevalence is approximately 12 %. In the age range 55–64 yr, the corresponding values are almost 40 % for males and 22 % for females. By means of questionnaires and ECG findings, it has been suggested from the British Regional Heart Study [1] that approximately one in five between the ages of 40 to 59 yr in England and Wales have severe ischaemic heart disease. Almost 60 % of this number involve men who are in their 50s and, in this category one in four may be regarded as suffering from severe ischaemic heart disease.

In recent decades, the mortality rate from IHD for both sexes in the U.K. increased gradually until the second half of the 1970s. Since then, however, there has been a small decline in mortality rate. In the U.S.A. and Japan the reduction in deaths from IHD has been particularly dramatic [2].

For comparison of different populations, the age standardized mortality may be used as an index. In 1980 the rates per 100 000 population for patients aged 40–69 yr were 482 (136) (male (female)) in the U.K. 398 (130) in the U.S.A., 314 (75) in West Germany, 386 (90) in Sweden and 65 (24) in Japan. These epidemiological data emphasize both the frequency and severity of IHD and stress that it is likely to feature very highly amongst anaesthesia-related morbidity and mortality in the perioperative period.

This Symposium Issue is designed to provide a recent review of the preoperative and perioperative problems presented by ischaemic heart disease, which represents not only one of the commonest major problems faced by the anaesthetist, but also a major socio–economic burden on the community.

There has been a great deal written in both the medical and the popular press on the cause of ischaemic heart disease. For the lay individual there should be little doubt that the principal risk factors for coronary heart disease are cigarette smoking, increased arterial pressure and increased serum concentrations of cholesterol. Established risk factors of less importance include concomitant diabetes and a family history of ischaemic heart disease and shortened life expectation. The greatest speculation and controversy have surrounded factors such as obesity, stress, personality type, hardness of tap water, and the extent of physical activity. Discussion of the aetiology of ischaemic heart disease is presented to open this Symposium Issue and this is followed by a review of recent advances in the drug therapy of acute and chronic ischaemic heart disease.

It is standard teaching that the incidence of postoperative myocardial infarction is increased when a patient has suffered a previous myocardial infarction and that the incidence is highest where the first infarction occurred within the 6-month period preceding surgery. This standard teaching is based upon large scale retrospective epidemiological reviews which were confounded somewhat by the appearance in 1981 of a study by Rao, Jacobs and El-Etr [3] which demonstrated that intensive invasive monitoring in the intra- and postoperative periods with treatment of haemodynamic instability could reduce the rate of postoperative re-infarction. These studies are described, with a discussion of the problems and pitfalls in interpretation of such data.

The high incidence of anaesthetic morbidity and mortality associated with ischaemic heart disease makes it essential to undertake a thorough preoperative assessment and investigation of the patient presenting for surgery. This area is considered in detail, with a discussion of the problems of proceeding to urgent surgery in patients with a myocardial infarction of less than 6 months duration.

In the early 1970s, there was great interest in the effects of anaesthetic agents and techniques upon the coronary circulation. Within a decade, it was clear from data obtained by several laboratories throughout the world that anaesthetic agents produced profound changes in coronary blood flow. However, with few exceptions, these changes occurred secondary to alterations in myocardial metabolic activity and no currently available agent (with the exception of isoflurane) has direct effects on the coronary vasculature. These studies were a prelude to the development of laboratory models of myocardial ischaemia for investigation of anaesthetic agents and techniques. In the past decade, a considerable body of information has accumulated, using a variety of models. On many occasions, apparently conflicting results have emerged; for example some studies have suggested that halothane has a beneficial effect on the ischaemic heart, whilst others have suggested a deleterious effect. In order to help the reader to resolve these conflicting data, this Issue contains a brief account of the different techniques which have been used for studying myocardial ischaemia, followed by a review of the effects of anaesthetic agents on these laboratory models. Whilst these studies have provided great insight into the pathophysiology and anaesthetic pharmacology of the ischaemic myocardium, they cannot provide quantitative guidelines on the clinical management of patients with myocardial ischaemia. Thus the remainder of our Symposium has been devoted to clinical studies of anaesthesia and myocardial ischaemia and a review of the anaesthetic management of patients for both cardiac and non-cardiac surgery.

Whilst the anaesthetist's major role in health care is the provision of a safe service for patients undergoing surgery, it is worth noting that he may also play a useful preventive role during his preoperative ward rounds by dispensing public health education, although this is thought usually to be the prerogative of the family doctor. There is good evidence for the effectiveness and economy of preventive interventions at the primary care level. For example, it has been calculated that the relative cost per "quality adjusted life year" (QALY) is £180 in terms of advice given by general practitioners to stop smoking, £1270 for coronary artery bypass graft (CABG) for severe angina with three vessel disease, £1700 for action by general practitioners to control hypertension, £2400 for CABG for moderate angina with three vessel disease, and £2400 for percutaneous transluminal coronary angioplasty for severe angina with one vessel disease and £8000 for heart transplantation [2].

G. Smith

REFERENCES

1. Shaper AG, Cook DG, Walker M, MacFarlane PW. Prevalence of ischaemic heart disease in middle aged British men. *British Heart Journal* 1984; 51: 595–605.
2. Wells N. *Coronary Heart Disease—The Need for Action.* London: Office of Health Economics.
3. Rao TLK, Jacobs KH, El-Etr AA. Reinfarction following anesthesia in patients with myocardial infarction: *Anesthesiology* 1983; 59: 499–505.

Br. J. Anaesth. (1988), **61**, 3–10

AETIOLOGY OF ISCHAEMIC HEART DISEASE

D. A. WOOD

Evidence on the aetiology of ischaemic heart disease (IHD) is derived in two ways, by observation and by experiment. The object of this paper is to review these sources of evidence in relation to smoking, arterial pressure and serum cholesterol concentrations.

OBSERVATION AND EXPERIMENT

Associations between smoking, arterial pressure and serum cholesterol concentrations and IHD were identified initially by observation in the general population. Cigarette smokers were observed to be at higher risk of IHD than those who chose not to smoke. Those with higher arterial pressure and serum cholesterol concentrations had a greater risk of IHD compared with those with lower values. Such observations may describe a causal relationship; alternatively, these factors may be confounders for the real cause of disease. For example, smoking may be associated closely with both the actual cause, say factor X, and the disease itself. In the absence of an experiment one can only judge if such relationships are causal or coincidental, and such judgements are necessary, as experimenting on the healthy population is unethical. Randomly assigning children in their teenage years to smoking and non-smoking groups, forcing the former to smoke cigarettes heavily for many years and prohibiting the latter from doing so, could answer a number of important scientific questions on whether or not smoking causes IHD, lung cancer, chronic airways disease and so on, but such an experiment could not, and rightly so, ever be undertaken. However, it is both ethical and practical to test the antithesis of such relationships; namely, if elimination of cigarette smoking and reduction of arterial pressure and serum cholesterol concentrations are associated with a corresponding reduction in the incidence of IHD.

First, evidence from observational studies of smoking, arterial pressure and serum cholesterol concentration will be described in relation to IHD. Then the evidence will be reviewed from unifactorial experiments undertaken to reduce these risk factors and the frequency of IHD.

Observational Evidence from Individuals

A prospective survey of individuals is necessary to measure the relationship between any biological factor and a disease. Such a study is based usually on a representative sample of a population—ideally, although it is never achieved in practice, a true random sample of the general population. Response rate to the initial screening survey should be as high as possible in order to avoid bias through non-response. Measurements are made with both accuracy and precision. Follow-up of all individuals over time is as complete as possible, with all cases of disease documented in a systematic and unbiased manner. Data from such a prospective survey are used to examine relations between biological factors measured at baseline, and subsequent risk of disease. There have been many such population studies of risk factors in relation to ischaemic heart disease, and one recent example from this country is the British Regional Heart Study.

This study [8] has reported on the relationship between smoking, arterial pressure, serum cholesterol concentrations and IHD, and was the first to do so for a representative sample of British men. In this prospective epidemiological survey, 7735 men aged 40–59 yr, drawn at random from the age and sex registers of general practitioners in 24 British towns were studied. From those selected for interview and examination, there was a 78 % response rate. A questionnaire was administered to provide demographic information, smoking habit, past medical history and so on, and the

---

D. A. Wood, M.Sc., M.R.C.P., University of Southampton, Royal South Hants Hospital, Graham Road, Southampton SO9 4PE.

following measurements were made by a team of Research Nurses: arterial pressure, body mass index (weight/height^2), serum lipid concentrations etc. All men were followed up and all cases of sudden death or acute myocardial infarction recorded. After a follow-up period of 4.2 yr, 202 cases had occurred in this population as a result of IHD. Relationships between several biological characteristics and the subsequent risk of IHD were examined; the results for smoking, arterial pressure and serum cholesterol are summarized below.

Smoking

Current cigarette smokers exhibited approximately three times the risk of IHD compared with those who had never smoked. Relative risk was calculated by taking a ratio of the probabilities, or odds, of IHD amongst cigarette smokers compared with those who never smoked. If no relationship existed between smoking and IHD the ratio would be unity. As the ratio increases the relationship is more likely to be causal than coincidental. In this study the ratio was 3, which implies that the risk of IHD amongst smokers is greater than those who never smoked, not just by 3%, or 30%, but by 300%.

After adjustment for the effect of other IHD risk factors, pre-existing ischaemic heart disease, and age, the relationship between smoking and IHD in this study remained virtually unchanged. A similar relationship between smoking and IHD has been shown in other population studies [6].

Arterial pressure

Both diastolic and systolic arterial pressures were related positively to risk of IHD. Unlike smoking habit, arterial pressure is distributed continuously, and to calculate IHD risk in the British Regional Heart Study men were ranked in order of magnitude of measurement, and then allocated into five groups of approximately equal size. The number of cases of IHD occurring in each quintile was used to calculate the probability of there being a case in each group. These odds were then expressed relative to men in the bottom quintile. For diastolic pressure, men in the top quintile of the distribution (diastolic pressure $\geqslant$ 90 mm Hg) had an estimated three-fold increase in risk of IHD relative to the bottom fifth ($\leqslant$ 72 mm Hg), while the remainder (72–90 mm Hg) were at intermediate risk.

For systolic pressure, there was an estimated two-fold increase in risk for the top 40% of men (systolic pressure $\geqslant$ 148 mm Hg) but there was no evidence of any trend at lower values.

Systolic and diastolic arterial pressure are so strongly associated it would be inappropriate to adjust one for the other when taking into account the effect of other variables. After adjustment for other IHD risk factors (except systolic pressure), and previous IHD, as well as age, the relationship between diastolic arterial pressure and IHD was largely unaltered. Similarly, the relationship between systolic pressure (without adjustment for diastolic pressure) and IHD was not altered significantly after adjustment for other risk factors.

A similar relationship for arterial pressure and IHD has been shown in other population studies [6] and, in common with smoking habit, it is judged to be causal.

Serum cholesterol

Total serum cholesterol concentration is related positively to risk of IHD and the British Regional Heart Study showed a continuous and marked trend of increased risk as the total concentration of cholesterol increased. Men in the top fifth of ranking for cholesterol (cholesterol $\geqslant$ 6.5 mmol litre^{-1}) had three time the risk of IHD compared with men in the bottom fifth, and men within the middle range of total cholesterol (6–6.4 mmol litre^{-1}) had almost double the risk of men in the bottom fifth.

After adjustment for the effect of other IHD risk factors, pre-existing IHD and age, the association of cholesterol with IHD remained highly significant.

A similar relationship between cholesterol and IHD has been shown in other population studies [6] and, in common with smoking habit and arterial pressure, the relationship between serum cholesterol concentration and IHD is judged to be causal.

Limitations of observational evidence

The independent associations between smoking, arterial pressure, and serum cholesterol concentration and IHD may be causal, or these factors may be confounders for the real cause of the disease. To judge such relationships—whether they are causal or merely coincidental—several criteria are used. These include the *strength* of association; *consistency*; if the association displays a *biological gradient*; *specificity* and the *temporal* relationship. Of all these, strength of association is probably the most important.

Relative risk measures strength of an association, namely the rate of disease in those exposed to a factor relative to the rate in those not exposed. For example, mortality rate from lung cancer in cigarette smokers is approximately 10 times the rate in non-smokers, a relative risk of 10-fold. To explain excess lung cancer among smokers by any factor other than smoking requires a factor so closely related to both smoking and disease that it should be detected easily. As no such factor has been identified, smoking is considered to be the principal cause of lung cancer. The larger the relative risk the more likely it is that the association is causal.

Consistency of an association implies that the same association has been observed in different populations, different places and at different times by different scientists using different methods, but with the same results. When the evidence for an association is consistent, such an association is more likely to be causal. A biological gradient, or dose–response curve between the degree of exposure and risk of disease implies that the association is more likely to be causal. Specificity of an association may apply to exposure or disease, or both, and the more specific a relationship the more likely it is causal. Finally, exposure must precede disease if the relationship is causal. Other criteria include biological plausibility of the association, coherence of all scientific evidence, and reasoning by analogy.

Applying these criteria to the associations observed between smoking, arterial pressure, serum cholesterol concentration and IHD, each is judged to be causal.

Experimental Evidence from Individuals

If smoking, arterial pressure and serum cholesterol concentration are considered to be related causally to IHD, what experimental evidence is there that elimination, or reduction of, such factors will reduce the frequency of disease? Unifactorial experiments have been conducted in relation to smoking, arterial pressure and serum cholesterol concentration and the results are reviewed below.

Smoking

Only one randomized controlled trial of anti-smoking advice in relation to mortality from IHD and other causes of death has been reported, and this was commenced in 1968 as part of the Whitehall Study [7].

Between 1968 and 1970, 16016 men aged 40–59 yr were screened during the Whitehall Study of London civil servants. Cigarette smokers ($n = 1445$) with the highest risk of IHD or chronic bronchitis, or both, based on a multivariate combination of risk factors were selected, and allocated randomly to two groups. In the intervention group, 744 men were recalled for individual advice. A large majority declared a wish to stop smoking and were supported to do so. No other advice was given except on calorie restriction for those who gained weight. The remaining 731 men served as a usual care group and were not recalled to receive specific advice on smoking, although a minority may have been advised not to do so by their general practitioner. The baseline characteristics of the two groups were comparable.

A dramatic reduction in reported consumption of cigarettes occurred in the intervention group; after a year it was 25 % of that of the usual care group. Thereafter, it tended to increase a little, whereas consumption in the usual care group declined slowly. The proportion of responders at the 1-, 3-and 9-yr follow-up survey who stated they were not smoking any cigarettes was 63 %, 57 % and 55 %, respectively. Over 10 years there were 251 deaths (table I) and the majority of these were attributed to IHD. No significant difference emerged between intervention and usual care in numbers of deaths from IHD, or any other specific cause; and there was no difference in all causes of mortality. The largest difference was seen for all cancer deaths, other than lung cancer, which were nearly 40 % higher in the intervention compared

TABLE I. *Randomized control trial of anti-smoking advice. Mortality results at 10 years*

	Intervention ($n = 744$)	Usual care ($n = 731$)	Proportionate change (95 % CL)
Ischaemic heart disease	49	62	18 % (−43 to +18 %)
Stroke	7	5	
Other cardiovascular	6	7	
Lung cancer	18	24	23 % (−58 to +41 %)
Cancers at all other sites	28	12	
Other causes	12	18	
All causes	123	128	2 %(−22 to +23 %)

TABLE II. *Randomized controlled trials of reduction in arterial pressure in relation to ischaemic heart disease*

		Number of events/population at risk	
		Treatment	Control
Veterans Administration Co-operative Study Group [9] Diastolic 115–129 mm Hg	All IHD	0/73	3/70
	Sudden death	0	1
	Fatal MI	0	0
	Non-fatal MI	0	2
	All-cause deaths	0	4
Veterans Administration Co-operative Study Group [10] Diastolic 90–114 mm Hg	All IHD	11/186	13/194
	Sudden death	4	8
	Fatal MI	2	3
	Non-fatal MI	5	2
	All-cause deaths	10	21
Australian National Blood Pressure Study [1] Diastolic 95–109 mm Hg	All IHD events	98/1721	109/1706
	Fatal IHD	5	11
	Non-fatal MI	28	22
	Other IHD events	65	76
	All-cause deaths	25	35
MRC Working Party Trial of Mild Hypertension [5] Diastolic 90–109 mm Hg	All IHD events	222/4523	234/4525
	Fatal IHD	106	97
	Non-fatal IHD	116	137
	All-cause deaths	248	253

with the usual care group, but this difference may have been produced by chance.

Therefore, although observational data strongly relate smoking to IHD, evidence from the only randomized control trial of anti-smoking advice showed no significant effect on death from IHD. Interestingly, the 18% reduction in IHD deaths (95% confidence intervals of −43% to +18%) seen in the intervention group is consistent with that observed in the British Doctors' Study, in which comparison was made between those who chose to stop smoking and those who continued to smoke cigarettes.

Arterial pressure

Three randomized placebo control trials of reduction in arterial pressure have been reported: the Veterans Administration Co-operative Study Group, Australian National Blood Pressure Study, and the MRC Trial of Mild Hypertension. The Hypertension Detection and Follow-up Programme is not considered here, because it was a trial of hypertension management rather than a placebo control study.

Veterans Administration Co-operative Study Group [9, 10]. In 1963 this group was formed to assess, by clinical trial, drug treatment of essential hypertension (excluding malignant hypertension) in relation to morbidity and mortality [9, 10]. A randomized double-blind placebo control trial was started in April 1964 to compare hydrochlorthiazide plus reserpine plus hydrallazine against placebo in male hypertensive patients with diastolic arterial pressures averaging between 90 and 129 mm Hg. Patients were randomized within pre-defined strata of diastolic pressure.

By 1967 the first report on 143 male hypertensive patients with severe diastolic hypertension, averaging between 115 and 129 mm Hg was published [9]. Twenty-two terminating events, mainly the development of retinal haemorrhages, exudates or papilloedema, but also dissection and rupture of aortic aneurysms, stroke and progressive renal failure occurred, one in those actively treated and the remaining 21 in the placebo group. Ischaemic heart disease was not a terminating event, but in this small group of patients three cardiac events occurred, all in the placebo group: two non-fatal myocardial infarctions and one sudden death without autopsy (table II).

Those 380 male patients with diastolic pressures between 90 and 114 mm Hg were reported in 1970 [10]. Again, there were fewer terminating events in the treatment group, approximately 25% of those in the placebo group, and these included deaths, other cardiovascular events such as cardiac failure and treatment failures, but not IHD. The latter was not a terminating event, but 24 such cases occurred: 11 in those treated actively and 13 in the placebo group, a difference which was not statistically significant (table II). As expected, within the range 90–114 mm Hg incidence of morbid events was lower in those with pre-randomization arterial pressure 90–104 mm Hg, and the beneficial effect of treatment was less than half that seen for those with diastolic pressure 105–114 mm Hg. The case for reducing arterial pressure to decrease the risk of IHD was not demonstrated by this study.

Australian Therapeutic Trial in Mild Hypertension [1]. A clinical trial of anti-hypertensive drug treatment on 3427 men and women aged 30–69 yr was commenced in Australia in 1973, defining mild hypertension as a diastolic pressure of 95 mm Hg or greater and less than 110 mm Hg, with a systolic pressure less than 200 mm Hg after two screening examinations [1].

Subjects were randomly assigned (with stratification for age and sex) to active treatment with chlorothiazide, and/or as second line drugs methyldopa, propranolol or pindolol, and as third line drugs hydrallazine or clonidine, all against matching placebo. Only 2218 subjects (64.7%) continued their trial regimen, either until a trial end-point occurred, or until the end of the study. The regimens were prematurely stopped by 1209, nearly 50% of their own volition, rather than on medical advice. Follow-up was for 4 years on average, and complete in the majority of patients.

IHD was the most frequently occurring trial end-point in both groups (table II) and the total number of IHD events was similar, as was the number of fatal events, non-fatal myocardial infarction and other manifestations of IHD (symptoms of angina, and the occurrence of ECG changes defined as ischaemia but not fulfilling WHO criteria of myocardial infarction). In common with the previous study, there was no evidence that reducing arterial pressure reduced the risk of IHD.

MRC Trial of Treatment of Mild Hypertension [5]. From 1977, 17354 patients with mild hypertension (diastolic 90–109 mm Hg) were recruited to this controlled trial of drug treatment, and this represented approximately 3% of those invited and screened [5]. Patients were allocated randomly at entry to one of four treatments: the thiazide diuretic bendrofluazide; placebo tablet similar in appearance to bendrofluazide; the beta blocker propranolol; and placebo tablet similar in appearance to propranolol. Stratification within blocks of eight within each sex, 10-year age group and clinic was part of the randomization procedure.

The therapeutic objective for those randomized to active treatment was to reduce diastolic pressure (phase V) to less than 90 mm Hg within 6 months of entry to the study. Compliance with treatment varied by sex, being better in women, and the cumulative percentage of people not taking either active drug by 5.5 yr was approximately 30%, which included both those who withdrew from their randomly allocated regimen, but continued on follow-up, and those lapsing from the trial.

In terms of control of arterial pressure, annual measurement showed the proportion of patients with diastolic pressure less than 90 mm Hg was consistently greater in the thiazide group compared with the beta-blocker group, and in both groups it was always greater than 60%, ranging from 60% to 79%. For the control group between one-third and one-half of those taking placebo had a diastolic pressure less than 90 mm Hg, although different subjects constituted this total at each annual review. Only 18% of the placebo group, for whom arterial pressure measurement at the first three annual visits was recorded, had diastolic arterial pressures less than 90 mm Hg on each of these three occasions. Approximately 22% of those randomized to placebo developed diastolic arterial pressures above the mild range, compared with only 1.7% of those receiving active treatment.

Coronary events were the most commonly reported end-point in this study (table II) and there was no difference between active treatment (taking bendrofluazide and propranolol together) and placebo in the total number of coronary events, or separately, the number of fatal and non-fatal coronary events. All-cause mortality was almost identical in the two groups. For coronary events, and for all-cause mortality, there were no statistically significant differences between the treatment effects of bendrofluazide or propranolol when examined separately.

In summary, none of the placebo control trials of reduction in arterial pressure has shown any benefit in terms of reducing the incidence of IHD, although all have reported a significant reduction in the frequency of stroke.

Cholesterol

Three primary prevention trials of reduction of serum cholesterol concentrations have been reported, all using a combination of diet and drug therapy: the WHO Co-operative Study, Lipid Research Clinics Coronary Primary Prevention Trial and the Helsinki Heart Study.

WHO Co-Operative Study [2]. This randomized double-blind controlled trial was commenced in 1965 to test the hypothesis that the incidence of IHD in middle-aged men could be reduced by decreasing their increased serum cholesterol concentration [2].

The study was carried out in three European centres—Edinburgh, Budapest and Prague. Serum cholesterol was measured in 15745 healthy male volunteers aged 30–59 yr, of whom 26259 were invited to participate. Subsequently, 15745 were assigned to three groups: 5331 men in the upper one-third of the cholesterol distribution were assigned at random to take ethyl chlorophenoxyisobutyrate (clofibrate); the other 50% of the upper one-third, numbering 5296, constituted a randomized control group taking identical capsules containing olive oil. A second control group of similar size, 5118, chosen at random from the lowest one-third of cholesterol distribution, also received olive oil capsules.

Men were recruited in different ways: from lists of blood donors, electoral rolls, tuberculosis survey registers and by advertising amongst the general public. Recruitment started in 1964 and was completed by March 1972, and the trial was completed by the late summer of 1976. The lifestyle of participants was not influenced intentionally, and there was no planned intervention in relation to other risk factors for IHD. The high serum cholesterol groups were almost identical in baseline characteristics.

Of the 5331 in the clofibrate group, 3586 completed 5 years of the trial, 1246 failed to continue for reasons other than medical, and those leaving the trial in the other two groups were of similar number.

There was a reduction of approximately 9% in serum cholesterol concentration (ranging from 7% to 11% in the three centres) over the course of the trial. This was associated with a 20% reduction in the incidence of all major IHD events (table III) in the treatment group compared with the high cholesterol control group; this reduction was confined to non-fatal myocardial infarctions, which were reduced by 25%. The incidence of fatal IHD was similar in the two high cholesterol groups, and there was no significant difference in the incidence of angina. The number of deaths from all causes in the clofibrate-treated group significantly exceeded those in the high cholesterol control group.

Lipid Research Clinics Coronary Primary Prevention Trial [4]. This double-blind placebo control trial tested the efficacy of reducing serum cholesterol concentration in the primary prevention of IHD.

Between July 1973 and July 1976, 480000 men aged 35–59 yr were screened, of whom 3810 healthy men were entered into the trial with a serum cholesterol of 6.8 mmol litre^{-1} or greater (the 95th percentile for men aged 40–49 yr) and with an LDL cholesterol concentration of 4.9 mmol litre^{-1} or greater, despite treatment with diet. Men with triglyceride concentrations averaging greater than 3.4 mmol litre^{-1}, or with Type III hyperlipoproteinaemia, were excluded; four men entered into the trial and found subsequently to have the latter disorder were removed from the study, two from each of the treatment groups.

Randomization was by the permuted block method, to two treatment groups within eight prognostic strata at each of 12 clinics. Baseline characteristics were essentially the same in the two groups. Subjects were prescribed either the bile acid sequestrant cholestyramine resin or an equivalent amount of placebo. Follow-up was for a minimum of 7 years and vital statistics for all men who originally entered the study were known. Compliance with treatment was similar in the two groups.

Average reductions in total serum cholesterol concentration and LDL cholesterol in the cholestyramine group were 13.4% and 20.3%, respectively, which were 8.5% and 12.6% greater

TABLE III. *Randomized control trials of decreasing cholesterol concentration in the primary prevention of ischaemic heart disease*

		Number of events/population at risk	
		Treatment	Control
WHO Co-operative Trial [2]			
Diet + clofibrate	All major IHD	167/5331	208/5296
Mean cholesterol	Fatal IHD	36	34
6.4 mmol litre^{-1}	Non-fatal MI	131	174
	All-cause deaths	162	127
LRC–CPPT			
Diet + cholestyramine	Definite IHD death and/or definite non-fatal MI	155/1906	187/1900
Mean cholesterol			
7.5 mmol litre^{-1}	IHD death	30	38
	Non-fatal MI	130	158
	All-cause deaths	71	68
Helsinki Heart Study [3]			
Diet + gemfibrozil	Definite IHD death and/or definite non-fatal MI	56/2051	84/2030
Mean cholesterol			
7.5 mmol litre^{-1}	IHD death	11	13
	Non-fatal MI	45	71
	All-cause deaths	45	42

than those observed in the placebo group. There was an increase in HDL cholesterol, and a larger increase in triglyceride concentration attributable to cholestyramine therapy.

The incidence of definite IHD deaths, definite non-fatal myocardial infarction, or both, was 19% lower in the cholestyramine group, and this difference was statistically significant (table III). The reduction was seen for both fatal and non-fatal manifestations of IHD. There was no significant difference in all-cause deaths between the two treatment groups.

Helsinki Heart Study [3]. This randomized placebo control study of 4081 middle-aged men (40–55 yr) with hyperlipidaemia was designed to investigate the effect of gemfibrozil, a fibric acid derivative, on the incidence of IHD.

Patients were selected from 23531 men employed by the Finnish Posts and Telecommunications Agency, the Finnish State Railways and five industrial companies in Finland. Of 18966 (80.6%) who agreed to participate in the screening, 4081 healthy men met the entry criteria and were willing to participate. All had non-HDL cholesterol (total cholesterol minus HDL cholesterol) concentrations $\geqslant 5.2$ mmol litre^{-1} on two successive measurements. Triglycerides were not measured in the initial screen. Random assignment to receive either gemfibrozil or placebo followed, and the two treatment groups did not differ in their baseline characteristics.

Of the 4081 randomized initially, 2859 (70.1%) continued in the trial until its completion, and the dropout rates in the gemfibrozil and placebo groups were comparable over time. Compliance judged by capsule counts was similar in the two groups. All subjects were followed for 5 years and included in the analysis; none was lost to follow-up.

In the gemfibrozil group, total serum cholesterol concentration initially decreased by 11%, LDL cholesterol by 10%, that of non-HDL cholesterol by 14%, and that of triglyceride by 43%; HDL cholesterol increased rapidly, by more than 10%. These changes were followed by consistent serum concentrations of total and of LDL cholesterol, and a small increase in triglyceride concentration, during the last years of the trial. The placebo group showed only minimal and random fluctuations from the baseline values.

The overall reduction in frequency of cardiac end-points in the gemfibrozil group was 34% (95% confidence intervals 8.2–52.6%) and this difference was explained almost entirely by a lower frequency of non-fatal myocardial infarction (table III). There was no statistically significant difference in the total number of deaths in the two groups and no significant differences between the groups in any specific non-cardiovascular causes of death.

Limitations of experimental evidence

A unifactorial experiment which reduces exposure to a risk factor and shows a corresponding reduction in the incidence of IHD is powerful evidence in support of the original association being causal. However, experiments to reduce risk of IHD also have their limitations. Elimination of, or reduction in exposure to, a biological factor does not necessarily reverse risk of disease in those who have already been exposed, and therefore a negative trial result does not negate evidence for causality from observational studies. In addition, the extent to which a risk factor is reduced may be too small to influence subsequent risk of disease. Risk factor reduction may be for too short a period, and follow-up in experimental trials may be too short to detect any benefit that may only be evident in the long term. In addition the alteration of risk factors may be too late in the natural history of the disease. Partial control of one risk factor in a multifactorial disease may be mitigated by the continuing presence of other risk factors. A negative trial may also, of course, be because the original association between a biological factor and disease was coincidental rather than causal. From the unifactorial clinical trials of cessation of smoking, reduction in arterial pressure and in serum cholesterol concentration, it is clear that experimental evidence for the relationship between cholesterol and IHD is strong, but not so for smoking and arterial pressure.

SUMMARY

There is evidence from population studies of strong positive associations between smoking, arterial pressure and serum cholesterol concentration and risk of ischaemic heart disease, and these appear to be independent of one another, but the evidence from unifactorial trials of risk factor reduction is less impressive.

For smoking, there is no good experimental evidence that cessation reduces the risk of IHD, but there are good observational data to show that those who choose to cease have a lower mortality from IHD, and all causes of death, compared with those who continue to smoke. For arterial pressure, none of the randomized controlled trials has shown any benefit from a reduction in arterial pressure in relation to IHD, although the same studies have shown that risk of stroke is reduced substantially.

The best trial evidence for risk factor reduction is seen for serum cholesterol, and in all three major placebo control trials, reduction was associated with a corresponding decrease in the incidence of IHD; for each 1% decrease in serum cholesterol concentration there was a 3% reduction in risk of IHD. However, total mortality was unchanged, and in the case of the WHO Co-Operative Study there was a statistically significant excess of deaths in the treatment group. The use of drugs in the primary prevention of IHD is a matter of judgement based on the risk of disease, the efficacy of the treatment and side effects.

REFERENCES

1. Australian National Blood Pressure Management Committee. The Australian Therapeutic Trial in Mild Hypertension. *Lancet* 1980; **1**: 1261–1267.
2. Committee of Principal Investigators. A co-operative trial in the primary prevention of ischaemic heart disease using Clofibrate. *British Heart Journal* 1978; **40**: 1069–1118.
3. Helsinki Heart Study. Primary prevention trial with Gemfibrozil in middle aged men with dyslipidemia. *New England Journal of Medicine* 1987; **317**: 1237–1245.
4. Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial Results. 1. Reduction in incidence of coronary heart disease. *Journal of the American Medical Association* 1984; **251**: 351–364.
5. Medical Research Council Working Party on Mild to Moderate Hypertension. MRC Trial of treatment of mild hypertension: principal results. *British Medical Journal* 1985; **291**: 97–104.
6. Pooling Project Research Group. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events. Final report of the Pooling Project. *Journal of Chronic Diseases* 1978; **31**: 201–306.
7. Rose G, Hamilton PJS, Colwell L, Shipley MJ. A randomised controlled trial of anti-smoking advice: 10-year results. *Journal of Epidemiology and Community Health* 1982; **36**: 102–108.
8. Shaper AG, Pocock SJ, Walker M, Phillips AN, Whitehead TP, Macfarlane PW. Risk factors for ischaemic heart disease: the prospective phase of the British Regional Heart Study. *Journal of Epidemiology and Community Health* 1985; **39**: 197–209.
9. Veterans Administration Co-Operative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. *Journal of the American Medical Association* 1967; **202**: 116–122.
10. Veterans Administrative Co-operative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. *Journal of the American Medical Association* 1970; **213**: 1143–1152.

Br. J. Anaesth. (1988), **61**, 11–23

MYOCARDIAL ISCHAEMIA: PROGRESS IN DRUG THERAPY

D. B. BARNETT

Ischaemic heart disease remains the major cause of morbidity and mortality in the Western World, accounting for more than 160000 deaths per annum in the United Kingdom alone. In recent years cardiac surgery for the management of ischaemic heart disease has become relatively commonplace. Thus most major regions of Great Britain are performing several hundred coronary bypass operations every year and very shortly there will be four main centres carrying out cardiac transplantation. At first sight these developments in surgical therapy might appear to overshadow apparently less exciting advances in cardiovascular drug therapy. However, new drugs introduced over the past 20 years have made very significant contributions to the management of all aspects of cardiovascular disease including hypertension, heart failure and hyperlipidaemia, in addition to angina and myocardial infarction.

In the management of acute and chronic ischaemic heart disease, over the past decade two main areas of drug therapy have emerged as of particular interest and potential. The first is the expansion and diversification of drugs which act on the calcium channel. The second is the increasing interest in the use of drugs during the very early phase of acute myocardial infarction in order to influence the development of the necrotic process and, hopefully, improve long term morbidity and mortality. It is these two aspects of drug therapy that will be dealt with in this review.

DRUGS ACTING ON THE CALCIUM CHANNEL

The introduction of drugs that antagonize the effects of calcium in the myocardium and the peripheral circulation probably represents the most exciting advance in cardiovascular therapeutics in recent years. If the 1970s were called the decade of the "beta blockers", then the 1980s will be remembered as the decade of the "calcium channel blockers".

Calcium is the most common cation in the body. Whilst its preponderance in the skeleton has been recognized for centuries, its presence in blood and other tissues was only shown when appropriate methods for measurement were devised. It is now known that the concentration of intracellular calcium is a critical factor in the regulation of both cardiac and peripheral vascular function.

The calcium channel

Calcium concentrations in the cytosol are in the micromolar range which is 1/100–1/1000 of the calcium concentrations in the plasma. Furthermore, this very small fraction of the body calcium within the cell is maintained by processes which make it independent of the normal variations of the extracellular calcium. Within the cell, calcium acts as the major regulator of a variety of cell functions, including the activation of the contractile proteins in both smooth and voluntary muscle. The free calcium concentration in the cell is controlled by regulation of calcium binding to intracellular organelles, in particular the sarcoplasmic reticulum and the passage of extracellular calcium across the plasma membrane through pores on the cell surface—the "calcium channels".

The dependence on these two processes is quantitatively different in different tissues. Thus skeletal muscle possesses a very highly developed internal recycling process for calcium binding and is relatively independent of external calcium for the control of contractile events. Conversely, the vascular smooth muscle and the myocardium are critically dependent on the availability of extracellular calcium and it is the controlled passage of this ion across the cell membrane through the calcium channels which regulates contractility in both these tissues.

In common with other ion channels, the calcium

D. B. BARNETT, M.D., F.R.C.P., Department of Pharmacology and Therapeutics, Clinical Sciences Building, Leicester Royal Infirmary, Leicester LE2 7LX.

channel is composed of a group of macromolecular proteins which traverse the bilipid layer of the cell membrane. Although very little is known of the exact nature of the channel, certain assumptions can be made on the basis of a large body of experimental work, leading to an overall concept of the structure. Thus since the channel is specific for a given ion species it is assumed that it must be provided with a selectivity filter. The channel opening is dependent also on the propagation of an action potential and membrane depolarization and thus it is also assumed to possess a voltage sensor which is a charged area of the channel protein that controls the opening of the channel "gates". Channels controlled in this way are referred to as voltage operated channels, in order to distinguish this process from the control of ionic channels by direct receptor mechanisms—the so-called receptor operated channels. The rate of influx is different for different ions and as this is slower for calcium than sodium, the calcium channel is also referred to as the "slow channel". Finally, it is also apparent that the protein molecular structure of individual channels is quite distinctive for each ion species, as drugs exhibit variable degrees of specificity in their interaction with different channels. The complex structure of the calcium channel has been studied extensively and exploited in the investigation of the action of different drug molecules in a search for specificity of drug effect at individual channels and between tissues.

There is now a considerable body of evidence supporting the existence of three structurally distinct classes of voltage sensitive calcium channels (called T, N and L) which are activated at different phases of the action potential and probably allow calcium to cross the cell membrane for differing time periods [30].

Calcium channel blockade

Calcium antagonism as a concept was pioneered first by Fleckenstein [8], who observed that verapamil mimicked the *in vitro* cardiac effects of calcium withdrawal and that this action was overcome in a competitive manner by increasing the concentration of extracellular calcium. At least seven different mechanisms of controlling cytoplasmic calcium concentrations have been identified and drugs which "antagonize" this biological response might, in theory, act at a number of different sites. The currently available calcium antagonists appear to act primarily by reducing calcium influx across the cell membrane by inhibiting the function of the "L" class voltage operated calcium channels [30]. As a group, therefore, these compounds should be referred to as "calcium entry blockers" or "calcium channel antagonists". However, for the purposes of this review these agents are termed "calcium antagonists" (Ca^{2+} antagonists).

These drugs exhibit considerable molecular heterogeneity and, as a result, classifying them into various groupings has been a subject of some debate. This is not just of interest to pharmacologists, but is of relevance in classifying modes of action of the various drugs in addition to potentially identifying clinically useful functional groups. The agents which are clinically of most importance at present are best classified into three groups (fig. 1) as follows:

Group 1: Phenylalkylamines (e.g. verapamil).
Group 2: Dihydropyridines (e.g. nifedipine, nicardipine).
Group 3: Benzothiazepines (e.g. diltiazem).

The Ca^{2+} antagonists have been characterized extensively *in vitro* in isolated cardiac and smooth muscle preparations in terms of electrophysiological and neuromuscular blocking properties. However, the overall clinical and haemodynamic effects are more relevant therapeutically in terms of the net effects on heart and circulation in the whole animal and man. Thus although the various drugs have similar qualitative effects *in vitro*, their net effects *in vivo* are quite different. This results from the interplay of the various direct effects and reflex responses which result from, for example, peripheral vasodilatation. Some of the more important comparative pharmacological properties of these agents *in vitro* and *in vivo* are listed in table I. Thus differences in therapeutic activity

TABLE I. *Properties of calcium channel blockers*

Property	Verapamil	Nifedipine	Diltiazem
Myocardial contractility			
In vitro	↓++	↓++	↓+
In vivo	↓+	↑+	↑↓
Relaxation of vascular smooth muscle	++	+++	+
Effect on heart rate			
Isolated atria	↓++	↓++	↓+
Intact organism	↑↓	↑	↓
Effect on AV conduction			
Isolated heart	↓+++	↓+++	↓+
Intact organism	↓+++	0 to ↑	↑↓

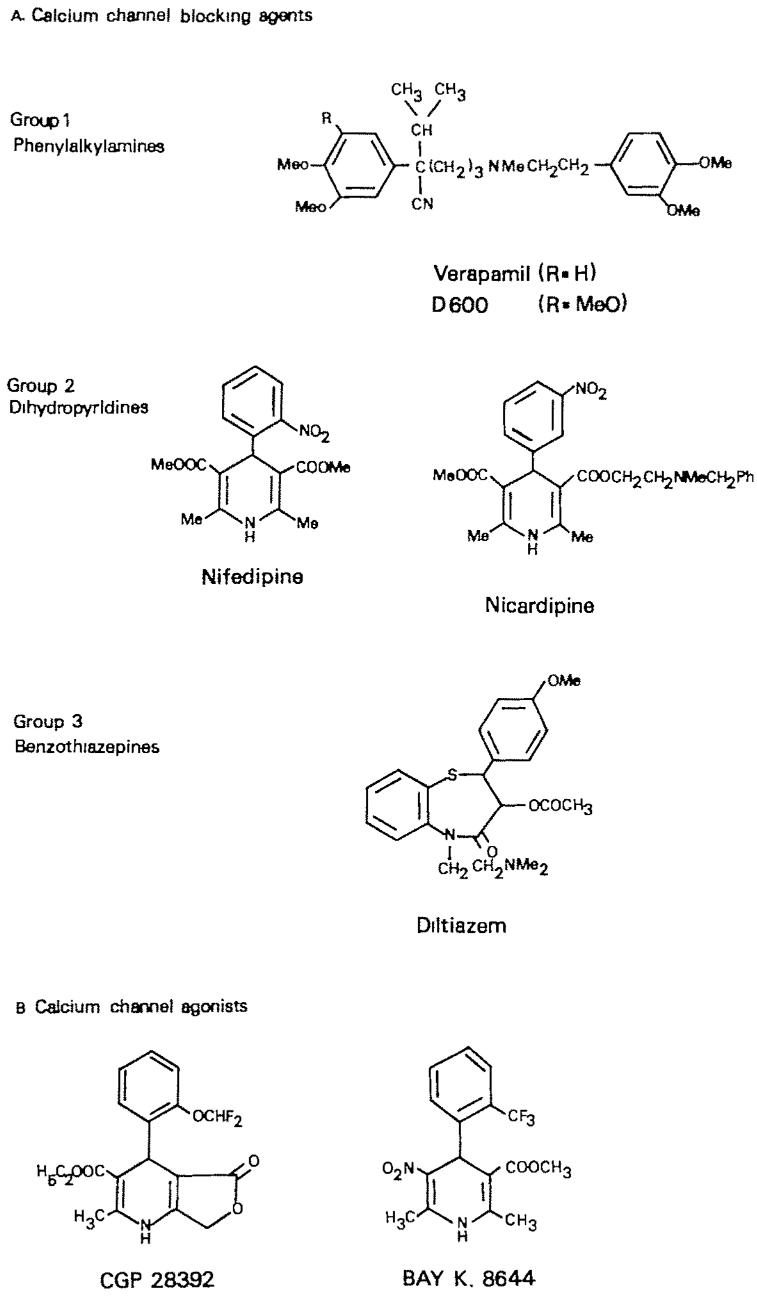


FIG. 1. Calcium channel blocking agents (A) and agonists (B).

are related to different quantitative effects of the drugs on cardiac and vascular smooth muscle function at clinically effective doses. This relative "selectivity" may have important future applications in the design of new drugs in this class and is discussed later.

Calcium channel blockade and ischaemic heart disease

The properties of the Ca^{2+} antagonists which are most relevant for the management of ischaemic heart disease are the vasodilator action on coronary and peripheral vascular smooth muscle (anti-anginal effects) and the possible prevention of ischaemic myocardial injury (cardioprotection).

Angina. Anginal pain results from imbalance of myocardial oxygen supply and demand. The Ca^{2+} antagonists exhibit a number of properties which are of potential benefit in this situation by affecting heart rate, peripheral vascular resistance (after load), coronary vascular resistance and myocardial contractility. The three major groups of Ca^{2+} antagonists are all effective antianginal agents and a choice between them depends on the presence of additional effects and adverse reactions.

Coronary artery spasm in the absence of structural abnormality of the vessel wall is the primary mechanism of Prinzmetals variant angina, leading to a reduction of coronary flow and angina at rest. Coronary vasospasm has also been recognized increasingly as a component of effort angina superimposed on the fixed narrowing of the arteries related to atherosclerosis, and possibly also as a primary event in some epiosodes of myocardial infarction [23]. The exact mechanism of the coronary spasm is unclear. It may be related to changes in autonomic tone in the coronary vessels, release of vasoactive substances such as 5-hydroxytryptamine or to the release of thromboxane from aggregating platelets. Whatever the cause, Ca^{2+} antagonists (particularly nifedipine) have proved of specific value in the management of this condition.

These drugs are, therefore, useful in all forms of angina, reducing the frequency and severity of attacks and consequently increasing exercise tolerance.

Cardioprotection. During the early phase of ischaemic injury, heart muscle fibres undergo characteristic alterations in metabolism and ultrastructural appearance which may be mimicked by and probably result from excess influx of calcium across the cell membrane, overloading the calcium binding capacity and calcium extrusion processes of the cell. These alterations result finally in necrosis. The crucial event in the development of the damage is related to deficiency of high energy phosphates, produced by excessive activation of calcium dependent intracellular ATPases, and calcium overload of the mitochondria which is manifest by swelling and vacuolation and the loss of metabolic activity.

Therefore, inhibition of calcium influx to the myofibrils during ischaemia by calcium channel blockade may favourably influence the outcome and protect the cells from irreversible damage. In addition, other properties of the Ca^{2+} antagonists that might be cardioprotective during acute infarction include effects on coronary vasospasm, antiarrhythmic activity and reduction of myocardial oxygen demand by inhibiting contractility, particularly in the ischaemic zone.

A large number of animal studies have suggested that the Ca^{2+} antagonists do exert a significant cardioprotective action in experimental myocardial ischaemia. Verapamil, nifedipine and diltiazem have all been investigated in a wide variety of animal models, indicating that treatment may have beneficial haemodynamic effects, increase collateral blood supply to the ischaemic area and reduce measurable indices of myocardial necrosis (for review see Kendall and Horton [19]). However, the data from these studies must be interpreted with caution. Thus drugs with vasodilator properties would be expected to have different effects in animals, such as dogs, that readily form a collateral circulation, compared with those that do not, such as pig, baboon and probably man [13, 26]. In addition, the effects of surgery and anaesthesia need to be taken into account in the animal experiments. Probably most important of all, the animal model is unlike the human disease in that the coronary arterial tree, except for the experimentally induced occlusion, is otherwise normal.

Several clinical trials have examined the possible protective effect of Ca^{2+} antagonists both during the early phase of acute myocardial infarction and as secondary prophylaxis against reinfarction. In the acute situation the drugs are tolerated to varying extents, with verapamil occasionally producing heart failure and nifedipine hypotension. In a large Danish multicentre study of acute infarction [5], verapamil was given first i.v. within 24 h of the onset of symptoms and then by mouth in a daily dose for 6 months. Of the 3498 patients allocated randomly to receive verapamil or placebo, there was no difference in either the number who progressed to proven myocardial infarction or in mortality rates at 6 months. The "Trent" study [34] enrolled 4491 coronary care unit patients who were allocated randomly to receive nifedipine or placebo within 24 h of admission. Treatment was initiated with a sublingual capsule followed by oral therapy for 28 days. In those patients with a definite in-hospital diagnosis of myocardial infarction, there was no significant difference in 1-month mortality between the two treatment groups (9.3 % and 10.2 % for placebo and nifedipine, respectively). Finally, the effect of diltiazem in 576 patients who had sustained non-full-thickness (non-Q wave) myocardial infarction was recently examined by the Diltiazem Reinfarction Study Group [10]. Treatment (diltiazem or matching placebo) was allocated randomly to begin within 24–72 h after the onset of symptoms and continued for 14 days. Diltiazem significantly reduced reinfarction and the incidence of "refractory" angina during the treatment period, both by approximately 50 %. However, there was no effect on overall mortality. These and several other smaller clinical trials suggest that the optimism engendered by animal studies for using calcium channel blocking drugs in early myocardial infarction has not so far been supported by clinical experience.

Selective effects of Ca^{2+} antagonists

The availability of radioactively labelled Ca^{2+} antagonists has facilitated the search for specific binding sites or "receptors" for these drugs and investigation of their mode of action. It now seems likely that the calcium channel is made up of three or four interlocking subunits and that the various groups of Ca^{2+} antagonists bind to distinct sites on this macromolecular structure [7, 25]. The channel, it is suggested, can exist in three separate but interconvertible states (open, closed or inactive) and there is good evidence from electrophysiological studies that the Ca^{2+} antagonists are able to interact differentially with these "states" by virtue of their different binding sites. Thus verapamil and diltiazem probably control the change from closed to open state, whereas the group 2 drugs (dihydropyridines, nifedipine-like) probably interact primarily with the open state of the channel and thus control the duration of "opening time". These differences may partly explain the functional selectivity of these drugs with reference to their effects on cardiac electrophysiology and smooth muscle contraction. Thus rapid interchange between closed and open state is probably of major importance in the coordinated transmission of the action potential through the specialized tissues of the heart. This is enhanced further at fast heart rates when the frequency of membrane depolarization is increased. The antiarrhythmic potency of verapamil increases under these circumstances—a phenomenon which is termed "use dependence". Conversely, the dihydropyridines exhibit this property to a far smaller degree and, consequently, are less effective antiarrhythmic agents. The duration of channel opening time may be more critical in the control of smooth muscle contraction, possibly explaining the enhanced vasodilatory properties of the nifedipine-like Ca^{2+} antagonists.

There are a number of other factors which may contribute to possible tissue selectivity of these agents, including: the number of binding sites present in different tissues; the relative importance of calcium entry through the slow channel as far as function of that tissue is concerned; and, possibly, pathological changes [25]. Of particular interest has been the exploitation of the molecular structure–activity relationships of the dihydropyridines in the development of drugs that have increased selectivity of action at different vascular beds and reduced direct effects on the myocardium. The dihydropyridine, nicardipine (fig. 1) is an example of one of these so-called second generation "non-negatively-inotropic" Ca^{2+} antagonists. This designation is a relative misnomer as, although at clinically effective doses these compounds are characterized by relatively selective action on vascular smooth muscle *in vivo*, they can still be shown to exhibit negative inotropism *in vitro*. The potential clinical relevance of this "vascular selectivity" is not yet certain, but the property represents an important innovative step in the development of these drugs.

Calcium channel agonists

Several newly discovered dihydropyridine derivatives appear to act as agonists at the calcium channel (fig. 1), increasing calcium influx and exhibiting positive inotropic effects in isolated heart preparations. Experiments examining transmembrane calcium currents in single cardiac cells can identify three "modes" of calcium channel gating, namely: brief transient opening—mode 1; long lasting opening with brief closure—mode 2; and no opening because of channel unavailability—mode 0. The calcium channel agonists appear to enhance calcium entry by promoting mode 2, whilst the Ca^{2+} antagonists inhibit current by favouring mode 0 [14, 22]. These discoveries open a new phase in the saga of calcium channel active drugs with the possibility of a new class of agents which may exhibit selective positive cardiac inotropic effects. In addition, the apparently wide variety of responses of the calcium channel and the action of calcium channel agonists gives cause to speculate that the dihydropyridines may have an endogenous counterpart that up-and-down modulates the calcium channel in a fashion analogous to the endorphins and the opiate receptor.

INFARCT SIZE LIMITATION AND THROMBOLYSIS

Reduction of Infarct Size

There are probably three main determinants of prognosis following myocardial infarction:

(a) the amount of myocardium lost;
(b) the presence of residual myocardium still vulnerable to ischaemia;
(c) an associated or separate liability to ventricular arrhythmias.

A number of clinical studies have borne out this direct relationship between the extent of myocardial infarction (that is, the amount of necrotic myocardium) and the early and late prognosis [9]. The extremes of this relationship can be seen as the development of cardiogenic shock which is associated with nearly 90% mortality when 40% or more of the left ventricle is infarcted, and the obvious benefits of complete prevention of infarction if the process is reversed at the earliest possible stage. The intermediate stages between these two extremes are not quite so clear cut, and several additional factors need to be taken into account. Thus limitation of the infarcted area may leave partially ischaemic and thus jeopardized or unstable myocardium. Patients in this situation of subendocardial or non-Q-wave infarction have a lower in-hospital mortality, but are more prone to reinfarction, usually in the same area as the original injury, and to potentially life-threatening arrhythmias generated from the remaining partially ischaemic myocardium [20]. In addition there are a number of other variables which either act independently or interact with the effect of infarct size on prognosis. These include age, sex, previous infarction and the presence or absence of heart failure [12]. Taken overall, however, there is considerable evidence supporting the importance of possible limitation of myocardial injury by therapeutic intervention during the first few hours after myocardial infarction.

Therapeutic strategies for infarct size limitation

During the past two decades infarct size reduction has been sought in both animal and human experimentation via a number of different approaches. These can be best classified into three main aims:

(a) the reduction of myocardial energy demands;
(b) the protection of the myocyte from ischaemic injury by direct action or by the stimulation of glycolytic energy production;
(c) acute reperfusion in order to re-establish the blood supply and hence oxygenation.

The effectiveness of these approaches in experimental animals has depended on a number of factors including the type of animal model, the duration and nature of the ischaemic injury and the method of evaluation of the amount of preserved myocardium. In general, however, the results from experimental coronary occlusion indicate that acute ischaemic injury can be limited by a variety of agents if administered early in the infarction process. This effect may be short lived for some drugs which appear to delay the development of the infarct rather than reduce the total quantity of necrotic muscle (for example, calcium channel blockers). These agents may be of use in providing a larger "window" of time during which other interventions may be possible to afford longer term protection.

The clinical effectiveness of these strategies has met with variable success, from the points of view both of reduction of early complications of infarction and of long term improvement in mortality. For the purposes of this review I shall concentrate on those interventions which are of particular recent and continuing interest in the clinical setting. These fall into classes (a) and (c) above—that is, early use of i.v. beta-blockade and acute coronary thrombolysis.

Beta blockade immediately after infarction

It is now well established that a reduction in mortality of approximately 25% can be achieved in the 2–3 years following myocardial infarction by the use of long term beta blockade [35]. Despite the various limitations of this therapy in patients with cardiac failure and respiratory disease, this approach to secondary prevention has become commonplace in most centres in the U.K. and elsewhere. More recently, attention has been centred on the use of beta blockers early during the process of infarction by administration i.v. within the first few hours after the onset of symptoms. It has been argued that this intervention may influence early arrhythmias and, by reducing myocardial oxygen demand, reduce infarct size and development. There is now a large body of published evidence attesting to the validity of this hypothesis [35]. Patients who present with characteristic chest pain suggestive of myocardial infarction, but who do not have the diagnostic ECG changes, have been described as having "threatened infarction". Two randomized controlled trials of such patients examining the effects of i.v. propranolol and atenolol have been carried out [27, 36]. Both studies indicated a significant reduction in the number of patients (approximately 50%) going on to develop full infarction in the treated *v.* the control groups. Although these results are derived from a selected group of subjects and cannot be directly applied to all patients suffering infarction, they indicate an important effect.

If infarction is not prevented does early beta blockade reduce the size of the final injury and does this have an effect on mortality in the short or long term? The answer to the first question is definitely yes. Thus data from more than 20 trials of various sizes indicate a reduction of infarct size (measured either by cardiac enzyme release or ECG parameters) following i.v. beta blocking drugs, providing treatment is begun within the first 12 h after the onset of pain [35]. Benefit has been described with a variety of beta blockers, suggesting that effect is largely a result of beta blockade as such and unrelated to ancillary properties such as membrane stabilizing effect, partial agonist activity or cardioselectivity. With regard to an effect on mortality, the trials can be separated into those which have used early i.v. beta blockers followed by long term oral treatment as part of a secondary prophylactic regimen, and those which have investigated the use of the i.v. route alone with no definite commitment to long term treatment. Data from trials of the former category do not indicate any important benefit related to beginning therapy by the i.v. route over and above that which would be expected from the long term effects of oral beta blockade used in these studies.

Recently two "supertrials" have addressed the question of the effect of early i.v. beta blockade alone on outcome in the short and the long term. These are the Metoprolol in Acute Myocardial Infarction study (MIAMI) [15] and the first International Study of Infarct Survival (ISIS) [16].

In MIAMI, 5778 patients from 104 hospitals were randomly designated to receive either metoprolol 15 mg i.v. followed by 100 mg by mouth twice daily, or placebo with treatment commencing within 24 h of onset of chest pain. Exclusions included patients older than 75 yr, those taking beta blockers or calcium antagonists, and the presence of heart failure, hypotension or significant bradycardia. After 15 days there had been 142 deaths (4.9%) in the placebo group and 123 deaths (4.3%) in the metoprolol-treated patients—a reduction of 13%, which was not considered significant. Some 2000 patients in this study were retrospectively defined as being in variable risk categories based upon the presence of a number of risk factors. These included age, abnormal ECG on admission, previous history of myocardial infarction, angina, heart failure, diabetes or prior therapy with diuretics or cardiac glycosides. Those patients who had three or more of these risk factors were said to be in a "high" risk group. In this group metoprolol therapy appeared to reduce 15-day mortality by approx. 25%, although the significance of this effect is uncertain in view of the method of retrospective analysis.

The ISIS trial was even bigger, and represents the largest intervention study ever performed; 16027 patients were included from 245 centres in 10 countries. Atenolol 5–10 mg i.v. immediately followed by 100 mg by mouth for 7 days was compared with conventional therapy in an open randomized study to which patients were enrolled within 12 h of the onset of symptoms. End points were both in-hospital and 1-year mortality and the exclusion criteria were similar to those used in the MIAMI study. After 7 days 313 treated patients (3.89%) had died compared with 365 controls (4.57%), a mortality reduction of 15% which, despite the wide confidence limits, was considered statistically significant. Of interest is the finding that the majority of this improvement in mortality was evident within the first 24 h (121 *v.* 171 deaths) but that, after 1 yr there was only a slight additional divergence between the groups (10.7% mortality in the atenolol group *v.* 12.0% control) and the difference at this time point was not statistically significant. There were a number of confounding issues in this study, as is characteristic of all multicentre trials, the most important being that patients initially assigned to atenolol treatment were more likely to be discharged on long term beta blockade (35 %) than those in the control group (25 %). The ISIS trialists concluded that the results of this study provide evidence of a highly significant effect on the combined end points of death, cardiac arrest and reinfarction in the first 7 days. They suggest that treatment of approx. 200 patients would lead to the avoidance of one death during this time period. However, it is debatable if that patient is any more likely to be alive at the end of 12 months without additional long term oral beta blockers.

In both MIAMI and ISIS beta blockers appear to have been well tolerated. This is almost certainly in part a result of pre-selection of patients, as is indicated by the low in-hospital mortality in the control groups (approximately 4–5 % in the MIAMI study). Thus in the MIAMI study only approx. 6000 of the original 26000 potential subjects admitted to hospital during the trial period were finally included in the trial. Similar figures for ISIS are not available, although it is estimated that approximately 20–25 % of admissions were included. Despite this degree of pre-selection, in the ISIS study immediate beta blockade increased the use of inotropic drugs during the first 24 h, although this did not appear to affect outcome. Nevertheless, the general applicability of this approach to treatment is limited, as beta blockade is probably contraindicated for haemodynamic reasons in approximately 30 % of acute cases and both trials excluded a large number of patients who were receiving prior therapy with cardioactive drugs and to whom the results of these studies cannot, therefore, be applied. Thus i.v. administration of beta blockers to selected patients early during the evolution of myocardial infarction is relatively safe and of modest benefit. Whether the long term benefit for these patients is sufficiently better than standard oral therapy with beta blockers, that routine use of the immediate i.v. route should be recommended, remains undecided.

Thrombolytic Therapy

Despite the recent interest in the contribution of coronary artery spasm to the production of both angina and myocardial infarction [23], there still remains a hard body of evidence linking the process of infarction to occlusive thrombosis in a coronary artery in the majority of patients. During the first few hours following the onset of acute symptoms, ischaemia evolves irreversibly to infarction unless blood flow is restored. In the majority of patients who survive to reach medical care, early angiography demonstrates the presence of thrombotic occlusion in at least one coronary artery [6]. Repeat angiography some days later shows that many of these occlusions disappear spontaneously. This almost certainly suggests that the occlusions were generated recently and probably represent the cause rather than the effect of the recent acute event. Reinstitution of coronary blood flow by clot dispersal (thrombolysis) and restoration of perfusion in the acutely ischaemic area as early as possible seems, therefore, to offer the most direct non-surgical approach to achieving reduced myocardial necrosis and possibly reduced immediate and longer term mortality.

Mechanisms of thrombolysis

It has long been recognized that blood from victims of violent death does not clot and would also render normal blood incoagulable, by digesting its fibrin. This "fibrinolytic" activity resides in the globulin fraction of the plasma. A beta globulin, plasminogen, is the inactive precursor of the proteolytic enzyme plasmin to which it is converted by a serine protease enzyme. Plasmin breaks down fibrinogen and fibrin both in the circulation and in recently formed clot. The exact mechanisms whereby a balance between coagulation and fibrinolysis maintains the blood in an appropriate fluid state are uncertain. However, there are available a number of therapeutic approaches to harnessing the fibrinolytic system, which are summarized in figure 2.

In 1945 Christensen and Macleod [2] showed that haemolytic streptococci produced an activator of the fibrinolytic system, which they termed streptokinase. This single chain protein of molecular weight 48000 Daltons does not activate plasminogen directly but complexes with it, and this complex is converted rapidly to plasmin. This mode of action is different from that of urokinase, which was identified first in the urine in 1885. Urokinase is also a beta globulin (mol. wt 54000 Daltons) which converts plasminogen to plasmin directly in a two-step reaction and is, therefore, best termed a plasminogen activator [29]. Streptokinase is antigenic, so that its administration may cause fever, arthralgia and possibly anaphylaxis, although this latter effect is rare. Urokinase is much less antigenic and so immediate side effects

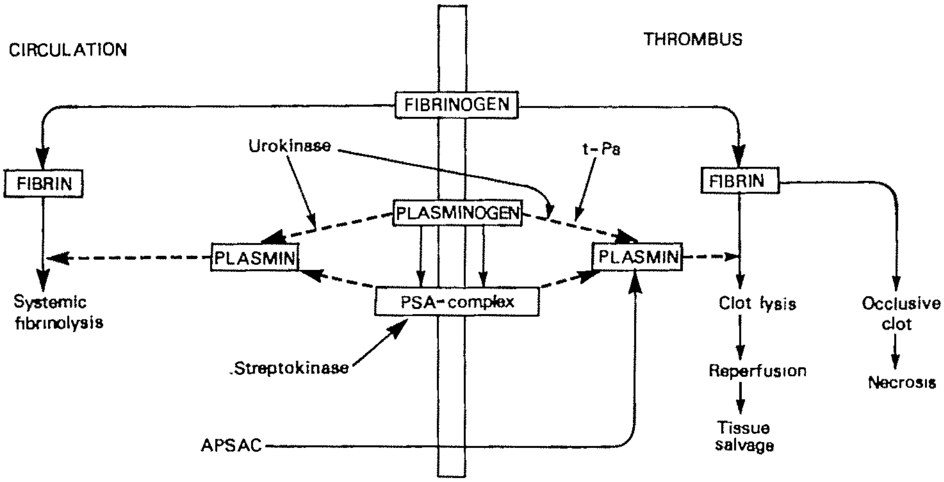


FIG. 2. Schematic representation of fibrinolytic system and action of various thrombolytic agents. Fibrin is formed from fibrinogen by the action of thrombin both in the circulation and in the developing thrombus. Fibrinolysis is produced by plasmin derived from plasminogen which binds to fibrin and fibrinogen. The rate of fibrinolysis is controlled by the deactivation of plasmin by α_2 antiplasmin (not shown) and by activation of the conversion of plasminogen to plasmin. This process can be activated either by tissue-bound plasminogen activators (t-PA) found in the endothelium of blood vessels, or by circulating compounds which act on plasminogen in blood and in recently formed thrombus. Urokinase is a direct plasminogen activator found in human urine. Streptokinase from haemolytic streptococci first binds to and complexes with plasminogen (PSA-complex) before conversion to plasmin, Anisoylated plasminogen–streptokinase activator complex (APSAC) may be protected in the circulation and preferentially act on clot fibrin avoiding the problems of systemic fibrinolysis (see text for details).

are fewer and it may be given for longer periods without stimulating neutralizing antibodies.

The activator of the fibrinolytic system, therefore, is plasmin, which attacks fibrin not only in a developing thrombus, but also in the larger pool of the circulation, which might lead to systemic fibrinolysis and uncontrolled bleeding. The natural. balance for this situation is provided by a circulating antagonist to free plasmin (α_2 antiplasmin). If the neutralizing capacity of this inhibitor is exceeded, as may occur with systemic use of streptokinase or urokinase, then indiscriminate fibrinolysis occurs.

Two new thrombolytic regimens are now available which attempt in different ways to circumvent these problems (fig. 2). The first is anisoylated plasminogen–streptokinase activator complex (APSAC). In this compound streptokinase and plasminogen are complexed together, but the active site of plasminogen is acylated, rendering the enzyme inert. After injection into the circulation, hydrolysis leads to deacylation, reactivating the plasminogen. Acylation does not abolish the affinity of the plasminogen for fibrin and APSAC is also unaffected by α_2 antiplasmin. The half-life of the deacylation process is approximately 40 min and so APSAC is relatively protected during its passage in the circulation to sites of recent thrombosis, where it binds to fibrin and after deacylation produces fibrinolysis. The deacylated compound is rapidly inactivated by α_2 antiplasmin and thus less systemic fibrinolysis would be expected. The second approach uses the ability of many tissues, including vascular endothelium, to produce powerful activators of the fibrinolytic system. This tissue plasminogen activator (t-PA) has a much lower affinity for plasminogen which is freely circulating than for plasminogen bound to fibrin, so that very little conversion of plasminogen to plasmin occurs in the general circulation, even at high plasma concentrations of t-PA. Thus like APSAC, systemically administered t-PA would seem to have "thrombus seeking" ability. Isolation of t-PA from human tissue cultures has proved very laborious but, with the recent use of recombinant DNA techniques, a material identical to human tissue plasminogen activator (rt-PA) can now be produced in much larger quantities [3].

Comparative effects of thrombolytic regimens in acute coronary thrombosis

I.v. and intracoronary streptokinase. Administration of a fibrinolytic agent directly into an occluded coronary artery would seem intuitively to be the best approach to coronary thrombolysis. There are a number of studies which show immediate efficacy of this direct lytic treatment by serial coronary angiography. Many of the early reports were on small numbers of subjects and it became obvious that, although patency was readily achieved, re-occlusion soon after fibrinolysis was common [24]. In addition, most of the original studies concentrated on patency rates rather than outcome. In 1983, however, the Western Washington group reported their initial results of a study of intracoronary (i.c.) streptokinase in 250 patients allocated randomly to active treatment or to conventional coronary care [21]. No specific post-streptokinase therapy was designated. The treatment was administered within 4–5 h after the onset of symptoms and patency of the occluded coronary artery was achieved in 68 % of the streptokinase group, compared with 12 % of the controls. A highly significant effect of streptokinase on mortality was seen when outcome was assessed over the first 1 month (table II). However, during long term follow up (up to 12 months) this initially favourable result had been considerably diluted with only a trend towards improved mortality after streptokinase therapy, but no statistically significant difference between the treatment groups (table II).

The use of the i.c. route for active fibrinolysis has, however, little relevance to the community problem of coronary care. The problems of carrying out immediate coronary angiography on all suitable patients seen within a few hours of the onset of infarction are enormous, let alone the potential dangers of the technique which would almost certainly restrict its use to subregional cardiology centres with access to cardiac surgery. Therefore, would the more readily applicable technique of i.v. administered streptokinase give acceptable efficacy from the points of view of both coronary reperfusion and outcome? Two direct comparisons of i.v. *v.* i.c. streptokinase in small numbers of patients have been published recently. Patients in both studies were assigned randomly to receive either approximately 2000000 unit of i.c. streptokinase over 1 h, or two different dose regimens up to 1000000 unit i.v., also over 1 h. Patency rates achieved were quite different for each trial. Thus Rogers and colleagues [28] showed angiographic restoration of flow in 76 % of patients receiving i.c. streptokinase, whereas the i.v. route achieved patency in only 44 % of patients receiving the highest dose of the drug. Conversely Anderson, Marshall and Askins [1] were able to re-open 70 % or more arteries by both regimens. Of interest was the finding in both studies that significant bleeding (requiring transfusion) was uncommon and occurred insignificantly more often in the i.v. group. Finally, there was a considerable difference in the average time interval from the onset of symptoms to commencement of therapy in each group reported in the trial by Anderson and colleagues [1] (2.8 h and 4.3 h for i.v. and i.c. administration, respectively) reflecting the inevitable delays inherent in the use of the intracoronary route. Comparative effects on mortality were not reported in these studies, although there were minor differences in ECG and cardiac enzyme patterns which tended on the whole to favour the i.v. route.

TABLE II. *Western Washington randomized trial of intracoronary streptokinase in acute myocardial infarction.* *P < *0.02. (Data from [18], [31]; see text for full description of trial)*

	Control ($n = 116$)		Streptokinase ($n = 134$)
Reperfusion (%)	12		68
Mortality (%)			
0–30 days	13 (11.2)	*	5 (3.7)
1 year total	17 (14.7)	(ns)	11 (8.2)

In order to answer effectively the question of the effect of streptokinase therapy on mortality after infarction, two much larger randomized studies have been mounted. The first of these reported in 1986 from Italy (the GISSI study [11]) was an unblinded trial in which 11806 subjects from a potential patient population of more than 31000 were assigned randomly to receive i.v. streptokinase in addition to the usual coronary care, or standard care alone. The effect on outcome was impressive, with overall in-hospital mortality at 21 days being significantly reduced by 18 % in the streptokinase-treated group. However, this effect was restricted almost entirely to those patients receiving streptokinase within 3 h of the onset of symptoms (mortality 9.2 % and 12.0 % in the streptokinase and control groups, respectively ($P < 0.01$)). This favourable outcome progressively disappeared in patients admitted at later time intervals, so that if therapy was delayed by more than 9 h there was no significant effect of streptokinase (mortality 15.8 % and 13.6 % in treated and control groups, respectively). Bleeding problems attributable to streptokinase were few (3.5 %) and those requiring transfusion very rare (< 0.5 %). Overall, the results suggested that i.v. streptokinase within 6 h of the onset of symptoms would substantially reduce early mortality in acute infarction with only modest side effects. However, the long term outlook for these patients is uncertain, as manifestly the causative obstructive arterial wall lesion remains unaffected by the thrombolytic therapy.

The second study is still in progress at the time of writing and has been set up by the ISIS group who initially evaluated the use of i.v. atenolol after infarction. The objectives of ISIS 2 are to evaluate early and late (up to 12 months) post-infarction mortality in a large (target 20000 patients), randomized placebo-controlled trial of i.v. streptokinase administered at various time periods up to 24 h after admission to hospital. Patients are also allocated randomly to receive treatment with low-dose aspirin after initial streptokinase treatment. Preliminary results on the first 4000 patients entering the trial within 4 h of admission have been published [18] and suggest that the active thrombolytic therapy significantly reduced 1-month mortality by approximately 25 %. This very important study is scheduled to finish recruiting patients in late 1987 and it is hoped that the final results will provide firm guidelines for future therapy.

TABLE III. *Comparison of i.v. streptokinase* v. *rt-PA in acute myocardial infarction. (European Co-operative Study Group) [13]. See text for details of trial.*

	Streptokinase	rt-PA
	1.5×10^6 unit for 60 min	0.75 mg kg^{-1} for 90 min
n	65	64
Patency rates (%)	55	70
Bleeding complications		
Total	39	21
Major (transfusion required)	5	4
In-hospital mortality	3	3
Plasma fibrinogen (%)	↓80	↓29
Plasma fibrin degradation products (%)	↑30	↑4.5

Newer fibrinolytic agents. A number of small trials of both APSAC and rt-PA in acute infarction have been reported over the past few years, with varying claims for efficacy. Both of these agents have convincingly been shown to produce reperfusion of acutely occluded coronary arteries and to reduce myocardial infarct size in placebo-controlled trials [4, 16, 32]. The theoretical advantages of these newer agents over streptokinase have already been discussed; however, convincing trial evidence of improved efficacy or reduction of bleeding complications in direct comparative studies with streptokinase has been lacking. Thus in one study by a European study group [33] a total of 129 patients were allocated randomly within 6 h of onset to receive either i.v. rt-PA or i.v. streptokinase (table III). The patency rates assessed by angiography were 70 % and 55 %, respectively, although the method of evaluation of the x-rays and blinding of the observers was suspect. Mortality was identical in the two groups and although bleeding complications were more common after streptokinase treatment, those deemed as serious problems, that is requiring transfusion, occurred with similar frequency (four patients *v.* five for rt-PA and streptokinase, respectively). Objective assessment of systemic fibrinolysis was also made with measurements of plasma fibrinogen and fibrin degradation products in the two groups, indicating a reduced systemic effect of rt-PA (table III). In the larger TIMI study [31], i.v. t-PA and streptokinase were compared in a total of 226 patients; a preliminary report of the findings of phase I of this study was published in 1985. In this trial patients were assigned randomly within 7 h of the onset of symptoms to receive either i.v. streptokinase or i.v. t-PA in varying doses over 3 h. All patients with characteristic chest pain and ECG changes, who were not excluded by virtue of potential bleeding or other hazards (recent CVA, peptic ulceration, shock etc.), were first submitted to coronary angiography. Only those subjects in whom demonstration of at least a 50 % reduction of the lumen of the infarct-related artery after intracoronary nitroglycerin were continued in the trial. In this somewhat pre-selected group reperfusion was once again achieved more readily with t-PA than with streptokinase (66 % and 36 % patency at the end of the infusions, respectively). In-hospital mortality was also less with t-PA (5 %) than streptokinase (8 %), although this difference was not statistically significant. Bleeding rates were similar and quite high in the two groups (43 % and 47 % for t-PA and strepto-

P25757

LIBRARY

kinase, respectively) although gastrointestinal bleeding was less with t-PA. Finally, extension of infarction or reinfarction during hospital admission occurred with approximately equal frequency in both groups. The TIMI study group concluded that t-PA provides a chance for favourably influencing outcome in the course of myocardial infarction, although reports on effects on long term mortality are still awaited.

Undoubtedly, we are entering an exciting phase in the investigation of acute coronary thrombolysis. However, the place for thrombolytic therapy in the treatment of acute myocardial infarction depends on more than recanalization rates of coronary arteries alone. It remains to be established if thrombolytic therapy can be delivered early enough by a simple and easily performed regimen to salvage ischaemic myocardium and if this effect on infarct size reduces morbidity and mortality at acceptable levels of side effect. At this time the results of i.v. streptokinase therapy are very encouraging, although benefit is most apparent in patients treated within the first few hours of the infarction process. In addition, the significant effects on mortality are restricted to the first 1 month and evidence for long term benefit is less convincing. Another as yet unanswered question is what to do after fibrinolytic therapy has been given if, as we suspect, thrombolysis simply extends the "window" of time during which other therapeutic measures can be used, directly or indirectly, to influence the underlying vascular pathology. These additional measures may include the use of anticoagulants, antiplatelet agents or early coronary angioplasty or bypass grafting.

Finally, the place of the newer fibrinolytic agents requires further careful evaluation, particularly in comparative trials with the present streptokinase regimens. It remains to be seen if these very much more costly agents will live up to their initial promise of improved efficacy and reduced adverse effects.

REFERENCES

1. Anderson JL, Marshall, HW, Askings JC. A randomised trial of intravenous and intracoronary streptokinase in patients with acute myocardial infarction. *Circulation* 1984; **70**: 606–618.
2. Christensen LR, Macleod CM. A proteolytic enzyme of serum: characterisation, activation and reaction with inhibitors. *Journal of General Physiology* 1945; **28**: 539–583.
3. Collen D, Stassen JM, Marafino BJ, Biulder S, De Look F, Ogez J, Tajiri D, Pennica D, Bennet W, Salna J, Hoyng C. Biological properties of human tissue type plasminogen activator obtained by expression of recombinant DNA in mammalian cells. *Journal of Pharmacology and Experimental Therapeutics* 1984; **231**: 146–152.
4. Collen D, Topol EJ, Tiefenbrunn AJ, Gold HK, Weisfeldt M, Sobel B, Leinbach R, Brinker J, Ludbrook P, Yasuda I, Buckley B, Robison A, Hutter A, Bell W, Spadaro J, Kahn B, Glossbard E. Coronary thrombolysis with tissue type plasminogen activator: a prospective randomised trial. *Circulation* 1984; **70**: 1012–1017.
5. Danish Study Group on Verapamil in Myocardial Infarction: Verapamil in acute myocardial infarction. *European Heart Journal* 1984; **5**: 516–528.
6. De Wood MA, Spores J, Notske R. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. *New England Journal of Medicine* 1980; **308**: 897–902.
7. Ferry D, Glossman H. Evidence for multiple-receptor sites within the putative calcium channel. *Naunyn-Schmeidberg's Archives of Pharmacology* 1982; **321**: 80–83.
8. Fleckenstein A. Specific inhibitors and promotors of calcium action in the excitation—contraction coupling of heart muscle. In: Harris P, Opie L, eds. *Calcium and the Heart*. London: Academic Press, 1971; 135–188.
9. Geltman EM, Ehsani AA, Campell MK, Schechtman K, Roberts R, Sobel B. The influence of location and extent of myocardial infarction on long term ventricular dysrhythmias and mortality. *Circulation* 1970; **60**: 805–810.
10. Gibson RS, Boden WE, Theroux P, Strauss HD, Pratt CM, Gheorghiade M, Capone RJ, Crawford M, Schilandt R, Kleiger R, Young PM, Schechtman K, Perryman B, Roberts R. Diltiazem and reinfarction in patients with non Q wave myocardial infarction. *New England Journal of Medicine* 1986; **315**: 423–429.
11. Giuppo Italiano per Lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986; **1**: 397–401.
12. Grande P, Nielsen A, Wagner G, Christiansen C. Quantitative influence of serum creatine kinase isoenzyme MB estimated infarct size and other prognostic variables on one year mortality after acute myocardial infarction. *British Heart Journal* 1985; **53**: 9–15.
13. Hearse DJ. Models and problems in the study of myocardial ischaemia and tissue protection. *European Heart Journal* 1983; 4 (Suppl. C): 43–47.
14. Hess P, Lansman JB, Tsien RW. Different modes of calcium channel gating behaviour favoured by dihydropyridine calcium agonists and antagonists. *Nature (London)* 1984; **311**: 538–544.
15. Hjalmarson A, ed. MIAMI; Metroprolol in acute myocardial infarction. *American Journal of Cardiology* 1985; **56**: 1G–57G.
16. Ikram S, Lewis S, Bucknall C, Sram I, Thomas N, Vincent R, Chamberlain D. Treatment of acute myocardial infarction with anisoylated plasminogen streptokinase activator complex. *British Medical Journal* 1986; **293**: 786–789.
17. ISIS 1 (First International Study of Infarct Survival) Collaborative Group. *Lancet* 1986; **2**: 57–66.
18. ISIS Steering Committee: Intravenous streptokinase

given within 0–4 hours of onset of myocardial infarction reduced mortality in ISIS 2. *Lancet* 1987; **1**: 502–000.

19. Kendall MJ, Horton RC. Are calcium antagonists cardioprotective. *Journal of the Royal College of Physicians* 1985; **19**: 85–89.
20. Kennedy JW. Non Q wave myocardial infarction. *New England Journal of Medicine* 1986; **315**: 451–453.
21. Kennedy JW, Ritchie JL, Davis KB, Fritz JK. Western Washington randomised trial of intracoronary streptokinase in acute myocardial infarction. *New England Journal of Medicine* 1983; **309**: 1477–1482.
22. Kokubun S, Reuter H. Dihydropyridine derivatives prolong the open state of calcium channels in cultured cardiac cells. *Proceedings of the National Academy of Sciences* 1984; **81**: 4824–4827.
23. Maseri A, L'Abbate A, Baroldi G, Chierchia S, Marzilli M, Ballestra AM, Severi S, Parodi O, Biagini A, Distante A, Pesola A. Coronary vasospasm as a possible cause of myocardial infarction: a conclusion derived from a study of "preinfarction" angina. *New England Journal of Medicine* 1978; **299**: 1271–1277.
24. Maukis JE, Malagold M, Parker A, Silverman KJ, Barry WH, Als AV, Paulin S, Grossman W, Braunwald E. Myocardial salvage after intracoronary thrombolysis with streptokinase in acute myocardial infarction. *New England Journal of Medicine* 1981; **305**: 777–782.
25. Naylor WG, Dillon JS. Calcium antagonists and their mode of action: an historical over-view. *British Journal of Clinical Pharmacology* 1986; **21**: 975–1075.
26. Newman DE. The coronary collateral circulation: determinants and functional significance in ischaemic heart disease. *American Heart Journal* 1981; **102**: 431–436.
27. Norris RM, Clarke ED, Sammel N, Smith W. Protective effect of propranolol in threatened myocardial infarction. *Lancet* 1978; **2**: 907–909.
28. Roger WJ, Manthe JA, Hoods WP, Baxley WA, Whitlow PL, Reeves CR, Soto B. Prospective randomised trial of intravenous and intracoronary streptokinase in acute myocardial infarction. *Circulation* 1983; **68**: 1051–1061.
29. Sobel GW, Mohler SR, Jones NW, Dowdy ABL, Guest MM. Urokinase: an activator of plasma profibrinolysis extracted from urine. *American Journal of Physiology* 1953; **171**: 768–769.
30. Spedding M. Three types of Ca++ channel explain discrepancies. *Trends in Pharmacological Sciences* 1986; **8**: 115–117.
31. The TIMI Study Group: The thrombolysis in myocardial infarction (TIMI) trial: Phase I findings. *New England Journal of Medicine* 1985; **312**: 932–936.
32. Van de Werf B, Ludbrock PA, Bergman SR, Tiefenbrunn AJ, Keith AA, Fox MB, De Geest H, Verstraete M, Collen D, Sobel BE. Coronary thrombolysis with tissue type plasminogen activator in patients with evolving myocardial infarction. *New England Journal of Medicine* 1984; **310**: 609–613.
33. Verstraete M, Bernard R, Bory M. Randomised trial of intravenous recombinant tissue type plasminogen activator versus intravenous streptokinase in acute myocardial infarction. *Lancet* 1985; **1**: 842–847.
34. Wilcox RG, Hampton JR, Banks DC, Birkhead J, Brooksby I, Burns-Cox C, Hayes M, Joy M, Malcolm A, Mather H, Rowlen J. Trial of early nifedipine in acute myocardial infarction: The Trent Study. *British Medical Journal* 1986; **293**: 1204–1208.
35. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomised trials. *Progress in Cardiovascular Diseases* 1985; **27**: 335–371.
36. Yusuf S, Sleight P, Ross PRF. Reduction in infarct size, arrhythmias, chest pain and morbidity by early intravenous beta blockade in suspected acute myocardial infarction. *Circulation* 1983; **67**: 32–41.

Br. J. Anaesth. (1988), **61**, 24–37

PERIOPERATIVE MYOCARDIAL INFARCTION

R. HAAGENSEN AND P. A. STEEN

The risk of developing myocardial infarction (MI) in connection with surgery and anaesthesia has been recognized for at least 75 years [19, 79, 93, 101]. Since then numerous reports have been published, some describing the incidence and characteristics of perioperative myocardial infarction (PMI), others the risk factors involved.

To compare these publications is difficult because of the great span in years between various studies, and the variability in study conditions such as selection and size of population, the use of a retrospective or a prospective approach, variations in postoperative care, the method of diagnosis of PMI etc. These factors can at least partly explain the variability and even contradictions observed in results. In most of these studies statistical evaluation also leaves much to be desired. The questions are often multifactorial, without the appropriate tests being performed. Performing simple chi-squared tests on whether sex, age, type or duration of anaesthesia etc, influence the infarction rate, does not provide a correct picture. There is often some co-variation between many of these factors, such as duration of anaesthesia and type of surgery. Thus the papers should be evaluated critically and the effects of a single factor reported in a single paper should be interpreted with caution.

Even more impressive, therefore, are the similarities in some of the results in spite of these differences in methodology, and certain trends appear in the literature that are important to the daily work of the anaesthetist.

In this review we have concentrated on the epidemiological aspects of PMI and the risk factors that have practical consequences in the treatment of patients. Frontline research concerning the pathophysiology of myocardial ischaemia and infarction and possible effects of different drugs are discussed elsewhere in this symposium issue.

Because of the paucity of information (with a few exceptions, such as the paper by Rao and colleagues [80]), we can only hint at perhaps the most important issue: will any diagnostic or therapeutic intervention change the outcome, and at what cost? These types of question are of vital importance to the Health Industry today. It is estimated that, every year in the United States alone, 1 million patients with documented ischaemic heart disease undergo a surgical procedure under anaesthesia. There is rapid development in our ability to diagnose and treat myocardial ischaemia. It is expensive to provide tests such as preoperative ECG, dipyramidole–thallium scintigram, preoperative stress test or coronary angiography for all the patients. What are their benefits? Should all patients at risk be monitored with pulmonary artery catheters; should they be placed in an intensive care unit (ICU) after operation? Should all patients with signs of myocardial ischaemia on a perioperative or postoperative ECG or ECHO be assessed for possible MI after operation? Such question are important. What is the cost: benefit ratio? In the North Sea oil industry an estimated £1.5 million are spent per life saved. How much can we allocate per life possibly saved in the context of PMI?

Perhaps these questions should be asked even before the studies are designed? This is even more controversial. Although freedom of research should be sacred, are we willing to accept the consequences supplied by the results? If some technique can reduce the operative mortality at the cost of £3 million per life, should the technique be implemented, or is the money better spent elsewhere? If we do not reach a decision ourselves, the medical technology industry, combined with our own fear of litigation, may soon make this a "standard of care". We feel that this point should be kept in mind when studying, and possibly implementing, results from the literature.

In this review PMI is defined as an infarct that

Rolf Haagensen, M.D.; Petter Andreas Steen, M.D.; Department of Anaesthesiology, University of Oslo, Ullevaal Hospital, 0407 Oslo 4, Norway.
Correspondence to P.A.S.

becomes apparent during the operation, or the first week after operation. There is a high incidence of MI throughout the first postoperative week, and as most of the studies in this field are retrospective, the exact moment of infarction often cannot be defined. This is especially true as a large number of the infarcts, varying from 21 % [96] to more than 60 % [6, 34, 94], are silent. The first indication of an infarction has often been cardiovascular collapse [76, 94], or hypotension or arrhythmia which have led the attending physician to investigate [6, 80, 94, 96]. It is, therefore, perhaps not surprising that PMI have been revealed throughout the peri- and postoperative periods. Steen, Tinker and Tarhan [94] reported that 25 % and Plumlee and Boettner [76] that 41 % of MI were discovered during the operation, while both Tarhan and colleagues [96] and Rao, Jacobs and El-Etr [80] reported a peak incidence on the 3rd day after operation.

INCIDENCE OF PMI

Some studies [3, 34, 40, 76] do not distinguish between patients with and those without previous MI, and report PMI rates varying from 0.08 % to 2.4 %, the highest tending to be in studies reporting mainly on patients with previous MI. In addition, the study by Baur, Nakhjavan and Kajani [6] reported an extreme 16 % incidence in 150 patients selected at random from a surgical list. From these and other studies, it soon became apparent that whether or not the patient had had a previous MI was the factor most profoundly affecting PMI rate. While Goldman and colleagues [40] undertook a thorough multifactorial analysis of risk factors, including previous MI, from the outset most other authors have classified the patients into those with and those without previous MI. In this review, evaluation of other risk factors therefore refers mostly to patients with previous MI, as the infarction rate in patients without previous MI is so low that it is difficult to obtain data that are statistically evaluable.

Patients without previous MI (table I)

A PMI rate of 0.65 % was reported by Knapp, Topkins and Artusio [57], and this study was later expanded, with the same results [98]. Others have later reported an incidence of 0.1–0.4 % [58, 88, 96].

Patients with previous MI (table II)

There is remarkable little variation in the overall PMI rate in these patients, varying between 3.2 % and 7.7 % for most of the studies, with a median mortality rate among those developing PMI of 70 %, independent of when it appeared in the postoperative course. There are a few exceptions to these data.

TABLE I. *Peri/postoperative myocardial infarctions in patients without previous MI*

Ref.	Authors	Years	Patients	Operations	PMI rate	Mortality	Type of study
[98]	Topkins and Artusio	1959–63	M > 50 yr	12054	0.66 %	27 %	Prospective
[96]	Tarhan et al.	1967–68	All > 30 yr	32455	0.13 %	69 %	Retrospective
[58]	von Knorring	1975–77	?	12497	0.20 %	36 %	Pro/retrospective
[88]	Schoeppel et al.	1980	All > 40 yr	928	0.40 %		Retrospective

TABLE II. *Peri/postoperative myocardial infarctions in patients with previous MI. *27 % of these patients had previously undergone CABG. None of these suffered PMI. If these are excluded, the reinfarction rate was 4.3 %*

Ref.	Authors	Years	Operations	PMI rate	Mortality	Type of study
[98]	Topkins and Artusio	1959–63	658	6.5 %	70 %	Prospective
[96]	Tarhan et al.	1967–68	422	6.6 %	54 %	Retrospective
[99]	Vormittag et al.	1965–72	334	7.5 %	92 %	Retrospective
[94]	Steen, Tinker and Tarhan	1974–75	587	6.1 %	69 %	Retrospective
[58]	von Knorring	1975–77	157	15.9 %	28 %	Prospective
[36]	Eerola et al.	1979	111	5.4 %	50 %	Retrospective
[88]	Schoeppel et al.*	1980	63	3.2 %	50 %	Prospective
[80]	Rao, Jacobs and El-Etr	1973–76	364	7.7 %	54 %	Retrospective
		1977–82	733	1.9 %	36 %	Prospective

TABLE III. *Reinfarction rate* v. *interval from previous MI*

Ref.	Authors	0–3 months	4–6 months	7–12 months	> 12 months	Unknown
[98]	Topkins and Artusio	55% (12/22)		25% (9/36)	3% (19/593)	43% (3/7)
[96]	Tarhan et al.	37% (3/8)	16% (3/19)	5% (2/42)	6% (20/353)	
[94]	Steen, Tinker and Tarhan	27% (4/15)	11% (2/18)	7% (2/31)	4% (17/430)	12% (11/93)
[58]	von Knorring	25% (4/16)		18% (2/11)	11% (10/89)	22% (9/41)
[36]	Eerola et al.	8% (1/12)	6% (1/17)	5% (4/82)		
[88]	Schoeppel et al.	0% (0/1)	0% (0/8)	0% (0/10)	6% (2/44)	
[80]	Rao, Jacobs and El-Etr					
	Retrospective	36% (4/11)	26% (8/31)	5% (6/127)	5% (10/195)	
	Prospective	6% (3/52)	2% (2/86)	1% (1/104)	2% (8/491)	

Von Knorring [58] reported a reinfarction rate of 16% in general surgical and orthopaedic patients with previous MI. He claimed that 40% of these infarcts would not have been detected without a prospective ECG study after operation, suggesting this to be part of the reason for the high reinfarction rate compared with the retrospective data from other studies. While this might be true, the number of silent infarcts was not greater in this study than in the retrospective studies, and many of the others with lower reinfarction rates were also prospective (table II). The mortality rate for PMI patients was low in this study (28%), making the mortality from PMI not different from that from the other studies.

All the above data have been challenged by Rao, Jacobs and El-Etr [80] and Wells and Kaplan [100]. In a retrospective study, the former group found a reinfarction rate similar to that reported by other investigators (tables II and III). This was reduced dramatically in a follow-up prospective study. The authors' findings were explained by their extensive haemodynamic monitoring and treatment of the patients in both the peri- and postoperative periods. More than 80% of the patients had pulmonary catheters and radial artery cannulae. Heart rates and arterial pressures were not allowed to fluctuate more than 20% from preoperative values, and arrythmias and tachycardias were treated immediately. The first 210 patients were monitored in the ICU for 24 h after operation with a 3.8% reinfarction rate. As in previous studies, many of the infarcts occurred later in the postoperative period, and the next 439 patients were therefore followed for 3–4 days, with a further significant reduction in the reinfarction rate to 1.4%. This study indicates that prolonged monitoring improves the results, despite the statistical objection presented by Lowenstein, Yusuf and Teplick [63] that the first 210 patients were made a control group because of the poor results.

Wells and Kaplan [100] reported no reinfarctions in 48 patients who had sustained a prior MI within 3 months of surgery. To our knowledge these data [55, 100] have not appeared in an original article yet. Ten percent of the patients in the study had previously undergone coronary artery bypass graft (CABG) surgery, but no further data are available on type of surgery, monitoring, definition of PMI, postoperative care, etc.

These reports do indicate that it is possible to reduce the high overall PMI rate in patients with previous MI. The questions are: at what cost and, if the expense is too high, which are the subgroups in whom more extensive monitoring and treatment would be more cost effective? Unfortunately, the level of uncertainty increases when one examines the influence of factors other than a previous MI on the PMI rate.

Interval from previous MI (table III)

The second most important factor in this multifactorial picture appears to be the interval from the previous MI. In all studies the reinfarction rate is greater if surgery is performed within 6 months of MI, with the highest rate occurring within the first 3 months. This was true even in the prospective study by Rao, Jacobs and El-Etr [80], which reported a low overall reinfarction rate.

Site of previous MI

Steen, Tinker and Tarhan [94] found no significant correlation between the PMI rate and the site of a previous MI. On the other hand, Eerola and colleagues [36] found that a previous posterior infarction was a significant risk factor, while Arkins, Smessaert and Hicks [3] found lower mortality rates if earlier infarction was subendocardial.

Other Factors Relevant to Coronary Artery Disease

Congestive heart failure

This has also been identified as a risk factor [26, 36, 40, 80]. In addition, Pasternak and colleagues [75] found a higher infarction rate in patients with a low preoperative ejection fraction (less than 35 %).

Angina pectoris

Angina is the main symptom of coronary artery disease (CAD). Patients suffering from angina pectoris run a higher risk of cardiac complications such as MI than the general population. It is, therefore, somewhat surprising that, although some authors report that many of the patients suffering a PMI had preoperative angina [6, 36, 76, 83, 96], most studies, including those with a more thorough multifactorial analysis, found stable angina not to be a significant independent risk factor [20, 26, 40, 58, 80, 94].

Coronary artery disease shown by angiography

Mahar and colleagues [67] reported that three-vessel disease was a significant risk factor for developing PMI.

ECG changes before and after operation (excluding signs of previous MI)

Many patients with CAD present with a normal resting ECG before operation. In patients admitted for peripheral vascular surgery, Tomatis, Fierens and Verbrugge [97] found that, among those with a normal resting ECG, 30 % (11/37) had severe CAD, with 75–100 % obstruction of a major coronary vessel, and 14 % (5/37) had a 50–75 % obstruction. Of these patients, some show typical ST-depression as a sign of myocardial ischaemia during exercise testing. Thus Cutler and colleagues [29] found that 73 of 100 patients admitted for vascular surgery had no ischaemic signs on a resting ECG, but 14 (19 %) of these had ischaemic signs during exercise testing. Of the 27 patients with signs of ischaemia on the resting ECG, 18 (67 %) had additional ST-changes during exercise. In these patients 48 operative procedures were performed, and PMI occurred in six, all of whom exhibited ischaemic signs on the exercise ECG. Arous, Baum and Cutler [4] similarly found that PMI occurred in 25 % of patients with positive preoperative exercise test who underwent major peripheral vascular surgery.

Von Knorring [58] reported that patients with preoperative ST-segment and T-wave changes, but no other indication of CAD, had a higher incidence of subendocardial infarction than patients with previous MI from history or ECG (12 % *v.* 6 %). Others [23, 70] have studied selected groups of patients with ischaemic heart disease and abnormal ECG before operation, and reported high incidences of a further deterioration in the ECG after operation, with a 4–9 % infarction rate.

Most authors have suggested that a preoperative ECG indicating pre-existing ischaemic heart disease is linked to perioperative cardiac complications [6, 20, 23, 26, 34, 49, 58, 70, 82]. On the other hand, Goldman and colleagues [40] found not ischaemic signs on the ECG, but preoperative arrhythmias (both ventricular and supraventricular) or recent MI, to be independent predictors of postoperative cardiac complications. Breslow and colleagues [14] reported that, while 19 % (71 of 394 consecutive patients) had ECG abnormalities 1 h after operation, nearly all were T-wave changes (flattening or reversal), and the incidence was not greater in patients with known CAD than in those without. In 70 of these 71 patients, the authors discovered no episodes suggestive of myocardial ischaemia in the postoperative period. They suggested that T-wave abnormality in the immediate postoperative period was a frequent event not linked to the development of cardiac complications and probably not a marker of myocardial ischaemia. Thus there is considerable difference of opinion as to the importance of T-wave abnormalities, particularly when they are transient. Driscoll and colleagues [34] used deeply inverted T-waves as the diagnostic criterion for PMI in 75 % of the cases. These changes were normalized in all patients followed up a few months later (four of nine patients). Thus the issue remains controversial.

Preoperative hypertension

This is defined very differently: either as a given arterial pressure value on a preoperative evaluation [26, 99] or as patients receiving antihypertensive medication [94]. There is a positive correlation between hypertension and ischaemic heart disease [54], and Prys-Roberts, Meloche and Foëx [78] reported that patients with untreated hypertension had the largest perioperative haemodynamic alterations which, again, has been reported to correlate with a high PMI rate (see below). It would therefore not be surprising if chronic hypertension also correlated with a high PMI rate, as reported by Eerola and colleagues [36], von Knorring [58], Steen, Tinker and Tarhan [94] and Vormittag and colleagues [99]. On the other hand, there was no significant correlation in the study by Rao, Jacobs and El-Etr [80] or that of Riles, Kopelman and Imparato [81] or in the multivariate analyses performed by Goldman and colleagues [40] and by Cooperman and colleagues [26]. Thus this issue also remains controversial. In the first group of studies the statistical evaluation might have been inadequate, with no sequential multivariate analysis, and the latter studies reported on smaller numbers of PMI with a greater possibility of incorporating a type-II error statistically.

Diabetes mellitus

Patients with diabetes have a two- to three-fold increase in prevalence of atherosclerotic disease [53]. Most authors have therefore included diabetes in their investigations of risk factors for PMI. To our knowledge, only Driscoll and colleagues [34] have suggested a possible connection (but without statistical analysis), and the statistical data seem to refute such a connection [40, 58, 70, 94, 99].

Age

The patient population is growing older and, with age, there is an increasing prevalence of ischaemic heart disease and associated diseases. This makes independent evaluation of age as a PMI risk factor more difficult, although Goldman and colleagues [40] reported that age exceeding 70 yr was an independent risk factor for development of cardiac complications. The population in a great number of the studies referred to here were patients with previous MI, and a patient who has experienced MI before the age of 30 yr must have a serious underlying disease. It is, therefore, perhaps not so surprising that approximately 50% of the authors [3, 34, 36, 80 (retrospective), 88] reported advanced age to be a risk factor, while the other 50% have not found a significant correlation [58, 80 (prospective), 89, 94, 96].

Sex

In one study the reinfarction rate was higher among men [96]; in another the mortality from PMI was greater among females [3]. Others have failed to find a sex-linked difference [40, 58, 80, 94, 99].

Risk indices

Some authors have attempted to combine all these (and other) factors to make risk indices as a tool for better preoperative evaluation of cardiovascular risks [26, 33, 40, 51, 86]. On this subject the reader is referred to the article by Goldman in this symposium issue.

Pre- and Peroperative Ischaemia

Although all data that have been referred to previously in this review have related to patients admitted to non-cardiac surgery, it is of interest to note that Slogoff and Keats [90], in their study of 1023 patients scheduled to undergo elective coronary artery bypass grafts (CABG) found no single or multiple preoperative patient characteristics to correlate with the PMI rate. What did correlate were signs of pre- and peroperative ischaemia. This is not surprising, since PMI must result from a disturbance in the oxygen demand:supply ratio, but this was the first time the relationship had been shown clearly in a large clinical series. PMI was almost three times as frequent in patients with ischaemia (6.9 *v.* 2.5%) and was independent of when ischaemia had occurred.

These ischaemic episodes (and thus PMI) were further correlated with tachycardia, but not with intraoperative hyper- or hypotensive episodes. There was, furthermore, a strong temporal relationship to anaesthetic or surgical events known to produce intense sympathetic stimulation, such as intubation and surgical stimulation.

Slogoff and Keats [91] have subsequently reconfirmed these results in another prospective study of 495 patients admitted for CABG, using different criteria for intraoperative hyper- or hypotension, because their first definitions were criticized by Lowenstein [62]. It is remarkable that approximately 50% of the episodes of myocardial ischaemia in the perioperative period were not associated with a marked change in systemic arterial pressure or heart rate. This is in accordance with the finding of Deanfield and colleagues [30], that only 23% of ischaemic episodes during daily life in patients with stable angina pectoris were preceded by heart rate increase of more than 10 beat min^{-1}. Thus although Slogoff and Keats [90] found the choice of anaesthetist to be closely correlated with the number of ischaemic episodes, at the present state of knowledge the anaesthetist does not, perhaps, have to feel guilty for every episode of ischaemia observed during anaesthesia.

Per- and Postoperative Factors Correlating with PMI Rate

Haemodynamic changes

Although there is no uniform definition of hypotensive episodes, most authors have reported an increased PMI rate (up to five-fold [94] with intraoperative hypotension [23, 36, 58, 70, 76, 80, 88, 99]. It could not be determined, of course, if the hypotensive episode was the cause of or a result of myocardial ischaemia. Rao, Jacobs and El-Etr [80] also found hypertensive episodes to be predictor of PMI, while the difference did not reach the significance level $P < 0.05$ in the study by Steen, Tinker and Tarhan [94].

Type of anaesthesia

The importance of choice of anaesthetist, rather than of anaesthetic agent, was stressed as long ago as 1928 [68]. While the choice of anaesthetist might be important, the choice of anaesthesia (regional *v.* general, different general agents) has not been shown to influence the PMI rate [3, 36, 58, 72, 94, 96, 98]. The only exception is an observation by Rao, Jacobs and El-Etr [80] in their prospective study, where the use of a nitrous oxide–opioid technique was associated with a significantly higher incidence of PMI than use of other anaesthetics. Whether or not the use of a nitrous oxide–opioid narcotic technique correlated with other risk factors was apparently not tested. Thus although the influences of different anaesthetics on the cardiovascular system vary, and some actions might have theoretical advantages, this has not been enough to cause differences in PMI rates in large epidemiological studies. For ophthalmic surgery under local anaesthesia or retrobulbar block, Backer and colleagues [5] found no PMI with 288 operations in patients with previous MI. The number of ophthalmic procedures performed under general anaesthesia was not large enough for a statistical comparison, but the study does indicate that this type of procedure and anaesthesia does not pose a special risk for PMI. McAuley and Watson [64] have also reported a lack of cardiac complications with 50 consecutive herniorrhaphies performed under local anaesthesia upon 45 patients with previous MI. However, as all the infarcts were more than 6 months old, the reinfarction rate suggested from the larger studies would be only 3–4%; thus the data are too few for appropriate evaluation.

Duration of anaesthesia and surgery

The influence of the duration of the procedure on the PMI rate is controversial. Von Knorring [58], Eerola and colleagues [36], Rao, Jacobs and El-Etr [80, prospective], Tarhan and colleagues [96] and Topkins and Artusio [98] all failed to find a correlation, while Arkins, Smessaert and Hicks [3], Rao, Jacobs and El-Etr [80, retrospective], Skinner and Pearce [89] and Steen, Tinker and Tarhan [94] all found a positive correlation, the last even with an increase from 2% for procedures lasting less than 1 h, to 17% for procedures lasting more than 6 h ($r = 0.994$). It is easy to be misled by statistics, however, and closer evaluation revealed, as expected, that the duration of the procedure and the type of surgery correlated. Consequently, the patients were classified into four groups: those with upper abdominal, intrathoracic and great vessel surgery lasting more than 3 h or less than 3 h, and other operations lasting more than 3 h, or less than 3 h. Then it became apparent that only patients with upper abdominal, thoracic or great vessel surgery lasting more than 3 h had a higher reinfarction rate than all others (16% *v.* 3–6%).

Site and type of surgery

These appear to be important risk factors for PMI. Eerola and colleagues [36], Goldman and colleagues [40], Rao, Jacobs and El-Etr [80], Steen, Tinker and Tarhan [94] and Tarhan and colleagues [96] all agree that there is a two- to four-fold increase in the PMI rate for thoracic and upper abdominal surgery compared with other sites, while von Knorring [58] did not find the site to be of significance.

Vascular surgery. Goldman and colleagues [40], Schoeppel and colleagues [88], Steen, Tinker and Tarhan [94] and Tarhan and colleagues [96] also

TABLE IV. *Peri/postoperative myocardial infarctions in patients admitted for vascular surgery*

Ref.	Authors	Operations	PMI rate	Mortality	Type of study	Note
[47]	Hicks et al.	298	10%	79%	Retrospective	Aortic aneurysms ruptured and elective
[4]	Arous, Baum and Cutler	102	25%	72%	Retrospective	Treadmill test positive
[45]	Hertzer	951	3.8% fatal MI		Retrospective	
[81]	Riles, Kopelman and Imparato	683	2.3%	31%	Retrospective	Carotid endarterectomy
[26]	Cooperman et al.	566	3.2%		Retrospective	Three × cardiovasc. complications with previous MI
[12]	Bernhard, Johnson and Peterson	15	13%	50%	Prospective	Carotid endarterectomy
[29]	Cutler et al.	48	12.5%	33%	Prospective	All MI occurred with positive exercise tests
[16]	Brown et al.	422	1.7% fatal MI		Retrospective	Aortic aneurysms, elective
[52]	Källerö et al.	380	5.5%	43%	Retrospective	
[51]	Jeffrey et al.	99	5%	20%	Prospective	Aortic aneurysms, elective

found a high PMI rate correlated with vascular surgery. These patients, who usually have generalized atherosclerotic disease, are known to have a high frequency of cardiac complications. Many studies have specifically addressed the problems in these patients without comparing them with other patient groups, and without restricting the studies to patients with previous MI [4, 12, 16, 26, 29, 33, 44–47, 51, 52, 97]. Even without selecting only patients with previous MI, the PMI rate in patients undergoing vascular surgery is high, varying from 2.3% to 25% in large series with mortality rates from 20% to 80% (table IV). The highest PMI rate, 25%, appeared in a series of patients who all had a positive ECG exercise test before operation [4]. That the rate seems as high in this patient population as in the general group with previous MI is perhaps not so strange: there is obviously a close connection between coronary artery disease and other vascular disease. Källerö and colleagues [52], who studied 380 patients for aorto–iliac or femoro–distal surgery found a 10% infarction rate (21/210) in patients with angiographic popliteal trifurcation disease, compared with 0% (0/170) in those without.

Because of the high incidence of concomitant arteriosclerotic heart disease in patients scheduled for vascular surgery, it has been suggested that coronary angiography and, if indicated, coronary artery bypass grafting (CABG) should be performed before other vascular surgery is contemplated [44–46]. Hertzer [44] reported a 59% incidence of significant anatomical coronary artery disease in patients with abdominal aortic aneurysms and no clinical evidence of ischaemic heart disease, increasing to 95% if the patients also had clinically suspected ischaemic heart disease. He also reported an overall mortality rate of 2.1% for 188 aortic and coronary operations in patients who had coronary angiography performed as a preoperative evaluation in patients with abdominal aortic aneurysms (AAA) or occlusive aorto–iliac atherosclerosis. Arous, Baum and Cutler [4] reported 25% PMI for vascular operations in 102 patients with positive treadmill tests, but no PMI in 14 patients who first underwent CABG. Brown and colleagues [16], on the other hand, found that only 1.7% (7/422) died after operation from PMI after elective operations for AAA at the Mayo Clinic in 1978–1980, although only six patients underwent CABG before their AAA surgery and 35% of the patients had previous MI. This mortality rate is no higher than that reported by Hertzer [46] and Brown and colleagues [16] did not find it justifiable to perform routine coronary angiography before elective AAA surgery. Furthermore, they found that only 2% (3/146) of the patients with previous MI died from PMI. This is much lower than reported previously from the same institution for the same procedures [94, 96].

PMI with Non-Cardiac Surgery in Patients with Previous Coronary Artery Bypass Grafts

In the past 15 years CABG has become a common procedure, and it is presently estimated that 20% of these patients may require some form of non-cardiac operations in the future. Therefore, studies not restricted to staged CABG/vascular surgery are appearing, to evaluate the cardiac risk from subsequent non-cardiac surgery in these patients. Unfortunately, the effect of previous CABG surgery on the PMI risk is difficult to evaluate from these studies; most do not have a control group, and most do not report the number of previous MI in the patients. Scher and Tice [85] produced the first report in 1976, with one probable PMI for 20 non-cardiac operations in patients with previous CABG. McCollum and colleagues [65] found no PMI after 77 operations and Edwards, Mulherin and Walker [35] reported 74 vascular procedures with no cardiac deaths. From these data, but without any statistical evaluation, it was suggested that patients with previous CABG not only are "acceptable risks" for surgery, but perhaps are even a lesser cardiac risk than the routine patients [65]. The conclusion that CABG can protect against cardiac complications and PMI in patients with ischaemic heart disease is shared by Akl and colleagues [2], Prorok and Trostle [77], Schoeppel and colleagues [88] and Crawford and colleagues [27]. The last study was of 358 patients with prior CABG, 70 of whom had an elective staged operation with a subsequent operation being performed 6–12 weeks after bypass, with no cardiac complications. The other operations were performed 10 days to 89 months after bypass, with three deaths and a significant number of cardiac complications (six MI), of which most occurred in patients subjected to the second operation within 30 days of CABG. The authors therefore suggest postponing elective surgery for at least 6–12 weeks after CABG.

A 6-month interval (as after an MI) was suggested by Cruchley and colleagues [28], who found that two of 121 patients with previous CABG infarcted, and that both PMI occurred within 6 months of the CABG. Patients operated upon within 6 months of the CABG had a 17% risk of cardiac complications, compared with only 2% and no infarcts if the interval was more than 6 months. Factors that increased the complication rate included congestive heart failure (33% complications) and surgery on the large vessels (40%).

In a restrospective study Mahar and colleagues [67] compared patients who had undergone CABG followed by a non-cardiac operation, with a patient group with angiographically demonstrated similar ischaemic heart disease who did not undergo CABG, but also required a non-cardiac operation. No PMI was seen after 168 operations in 99 patients with CABG, 65% of whom had a previous MI, whereas there was a 5% incidence of PMI with 58 operations in the 49 patients treated only medically, of whom a similar proportion (63%) had a previous MI. The authors did not exclude the possibility that the intervening CABG consisted of a "survival test" or caused MI in those patients who might not otherwise have had an MI after the non-cardiac operation.

The combined results of all these studies do seem to indicate that survivors of CABG appear to be reasonably good cardiac risks for subsequent operations, at least if surgery is postponed for some time (6 weeks to 6 months?). The merit of elective surgery with prophylactic CABG is not established and, as pointed out by Schoeppel and colleagues [88], there are no studies of PMI with non-cardiac surgery being performed more than 5 years after CABG. The long term prophylactic effects of CABG surgery are currently unknown and may be different because of continued progression of the coronary artery disease.

Perioperative Myocardial Infarction (PMI) in Relation to Coronary Artery Bypass Grafting

The goal of CABG is to improve coronary blood flow and thereby relieve angina and prevent myocardial damage in patients with ischaemic heart disease. As mentioned above, the CABG procedure itself is associated with a certain myocardial damage and operative mortality, dependent on multiple interrelated variables of patient characteristics and perioperative management methods.

Diagnosis

The diagnosis of PMI in association with CABG may be difficult. Three factors commonly used as good indicators of PMI are serial ECG, serial cardiospecific enzyme liberation assessments and serial technetium 99-m-labelled pyrophosphate scans, all of which have limitations and possibilities for misinterpretation of the results [7].

ECG. The appearance of new Q-waves of 0.04 s or more duration is an accepted criterion of transmural myocardial infarction. The existence of old Q-waves or bundle branch blocks limits the usefulness of this criterion. Furthermore, the occurrence of new Q-waves in the inferior leads after CABG has been claimed, in some cases, not to present a new MI, but rather the unmasking of a pre-existing infarction [8]. Subendocardial infarctions manifest themselves through changes in the ST–T segment. Observation of transient changes in that segment is a common phenomenon after revascularization, probably because of postoperative pericarditis or metabolic alterations, and cannot be used in the diagnosis of PMI. In general, the use of new Q-waves as the only criterion of MI after CABG underestimates the frequency of its occurrence.

Enzymes. Serial creatine phosphokinase isoenzyme (CK mb) concentrations obtained before operation and at well defined intervals during the postoperative period, are frequently used to measure myocardial damage after CABG. A certain amount of enzyme release always occurs following revascularization, probably because of surgical trauma to the heart, ischaemic injury to the cells, washout from previously jeopardized myocardium, lung damage, haemolysis or defibrillation [31, 32, 42, 60, 66]. Thus the peak increase in CK mb is of limited value. The enzyme release from patients with severe myocardial damage (infarction) is characterized by a high peak and a prolonged release, and thus the measure of total CK mb liberation gives the most reliable result in the diagnosis of PMI [32].

Radionuclide imaging. Myocardial cell death is accompanied by cellular influx of calcium ions which localize within the mitochondria in the crystalline structure, hydroxyapatite. By using 99-m stannous technetium pyrophosphate, scintillation images of recent myocardial infarction can be produced [13] and this is used widely for the detection of new MI after CABG [17, 69].

There is no clinical "gold standard" for the diagnosis of perioperative myocardial infarction in association with CABG. When using all three of these diagnostic tests (ECG, enzymes and scanning) it is commonly concluded that a patient has suffered PMI when at least two tests are positive. One positive test alone, is regarded as a false positive [7, 60].

Frequency and consequences of PMI

The occurrence of, diagnostic criteria for and mortality from PMI are listed in table V. In these CABG patients PMI is a serious event, with mortality rates varying between 3% and 34% [21, 37, 41, 42, 84, 92] and it accounts for almost 50% of the mortality during CABG. The occurrence of PMI is associated also with arrhythmias, cardiac insufficiency and a longer stay in the ICU [9].

While there is little disagreement that PMI is associated with higher morbidity and mortality in the immediate postoperative period, the long term consequences are controversial. Bateman, Matloff and Gray [9] claimed that, while PMI may confer an ominous short-term outcome, the long term prognosis might be essentially benign, as most of the PMI are small electrophysiological events, thus explaining the lack of influence on long term clinical status or mortality. This is in agreement with the data of Codd and colleagues [24], Gray and colleagues [41] and Balderman and colleagues [7]. On the other hand, Chaitman and colleagues [22], Fennell and colleagues [38], Hacker and colleagues [43] and Namay and colleagues [73], in their follow-up studies, claimed that long term survival is significantly shorter in patients who suffered PMI compared with those who did not, even when allowance is made for the higher perioperative mortality rate in the former group. In the CASS-report on 9777 patients who underwent CABG between 1974 and 1979 [84], actuarial survival, including hospital deaths, at 1, 3 and 5 years was significantly greater in patients without infarction than in patients with PMI (96%, 94% and 90% *v.* 78%, 74% and 69%).

Variables associated with an increased risk of PMI

As with patients admitted for non-cardiac surgery, there is much controversy in the literature regarding preoperative variables that might predispose to PMI during CABG. According to various authors [11, 43, 66, 87, 90], age and sex are not risk factors for developing PMI during revascularization. The CASS studies [39, 84] indicated that age older than 65 years was associated with both a higher perioperative morbidity, including MI, and mortality, but there was no difference between the sexes in this older age group. Patients older than 65 years had a significantly higher incidence of multiple chronic medical diseases, thus it was difficult to single out age *per se* as a risk factor. On the other hand, previous illness such as hypertension or previous MI, diabetes mellitus or preoperative use of betablockers or anticoagulants have not been found to

TABLE V. *Peri/postoperative myocardial infarctions in connection with CABG surgery*

Ref.	Authors	Years	Operations	PMI rate	Mortality	Study	ECG	Enzyme	Scan	Myocardial protection
[43]	Hacker et al.	69–78	1341	3.8%	26%	Retrosp.	+	–	–	Systemic hypothermia + topical cooling
[61]	Lim et al.	1973	1582	6.2%	5–7%	Prosp.	+	(+)	–	
[71]	Miller et al.	71–75	1000	8.7%		Retrosp.	+	(+)	–	After 1973 topical hypothermia ± cold cardioplegia
		77–79	973	4.6%		Retrosp.	+	(+)	–	
[41]	Gray et al.	75–76	225	13.7%	(3.2%)	Prosp.	+	+	+	Systemic hypothermia
[11]	Bedard et al.	75–76	198	9.1%		Prosp.	+	–	–	Normothermic arrest
[59]	Levinsky et al.	74–76	404	5.9%		Retrosp.				Hypothermia
		76–78	843	3.9%		Retrosp.				Cardioplegia
[7]	Balderman et al.	77–78	103	8%		Prosp.	+	+	+	Cold cardiplegia or intermittent cross-clamping
[38]	Fennell et al.	79 (publ.)	100	17%		Prosp.	+	+	+	Hypothermia
[21]	Chaitman et al.	1978	1340	4.6%	9.7%	Prosp.	+	–	–	Variable (10 hospitals)
[84]	Schaff et al.	74–79	9777	5.7%	19%	Prosp.	+	+	–	Variable (15 hospitals)
[42]	Guiteras Val et al.	80–81	112	13.4%	13.3%	Prosp.	+	+	+	Cold cardioplegia
[90]	Slogoff and Keats	81–82	1023	4.1%	12.0%	Prosp.	+	+	–	Cold cardioplegia
[91]	Slogoff and Keats	86 (publ.)	495	4.2%	9.5%	Prosp.	+	+	–	Cold cardioplegia
[10]	Baur et al.	80 (publ.)	102	15%		Prosp.	+	+	+	Topical hypothermia or ± cardioplegia
[37]	Eugene et al.	80–82	207	11%	34%	Prosp.	+	+	+	Hypothermia Blood cardioplegia
[60]	Li et al.	82–84	212	14.6%		Prosp.	+	+	+	Cold cardioplegia
[66]	McGregor et al.	84 (publ.)	50	14%	29%	Prosp.	+	+	+	Systemic hypothermia or cold cardioplegia

be independent risk factors for PMI in these patients [22, 39, 86, 90]. Unstable angina was not associated with a higher incidence of PMI compared with patients with stable angina in the studies by Schneider, Pichard and Mindich [87] and Hultgren and colleagues [48], while Fennell and colleagues [38] and Gersh and colleagues [39] found a significant associated between unstable angina and PMI.

Patients with severe pathology of the coronary tree and decreased ventricular performance have a higher risk of developing PMI. Angiographic findings of left main coronary artery stenosis, high LVEDP or a decreased ejection fraction are all associated with a higher incidence of PMI [10, 42, 71].

Methods for intraoperative management. The PMI rate increases with duration of cardiopulmonary bypass [10, 21, 42, 74]. The myocardial preservation technique used during aortic cross clamping is of great importance [1, 10, 24, 25, 56, 92]. The technique with cold potassium cardioplegia currently used is claimed to be among those factors that have contributed most to the reduction in the frequency of PMI during CABG [56, 59]. This must be seen in connection with the duration of ischaemic cardiac arrest, as an arrest time of more than 40 min increases PMI rate [42, 43, 90, 92]. The surgical technique, number of grafts and graft flow seem to be of importance [11, 42, 74, 90]. Although Slogoff and Keats [90] found that the quality of a distal anastomosis, as rated by the operating surgeon before removing the aortic cross clamp, was one of the independent predictors of PMI, graft occlusion *per se* does not seem to influence the PMI rate [15, 18, 24, 38].

Two distinct types of necrosis have been found by histological and electron microscopic studies in patients with PMI. First, ordinary coagulation necrosis found in areas with transmural infarction supplied by an occluded graft. Second, contraction band necrosis found in infarcted areas supplied with narrow native vessels, poorly developed collateral vessels and wide open grafts [15, 18, 95]. This contraction band necrosis is seen experimentally when a coronary artery is occluded long enough to cause severe ischaemic changes within the muscle cell before reperfusion [95]—a situation probably not different from that found during CABG when the metabolic protection during aortic cross clamping distal to a severe stenotic vessel is inadequate.

That an area of the myocardium may become ischaemic or damaged during CABG even before the patient is on cardiopulmonary bypass has been demonstrated by spillage of cardiospecific enzymes or ischaemia on the ECG [50, 74, 90].

CONCLUSION

In high risk groups of patients, especially those with previous myocardial infarction, the risk of developing and the mortality from perioperative myocardial infarction is high. It seems possible to reduce this risk by the use of "intensive" monitoring and immediate intervention when haemodynamic abnormalities occur. We still believe it is wise to postpone surgery until 6 months after myocardial infarction, if possible. As with all the other risk factors mentioned in this review, this factor must be evaluated when consulting with the patient on whether or not he or she should undergo surgery and anaesthesia. The risks of operating should always be evaluated against what is likely to happen if the patient does not undergo surgery. The possibility of reducing myocardial ischaemia and infarction in the peri- or postoperative period should be closely scrutinized in a cost–benefit evaluation.

REFERENCES

1. Akins CW. Noncardioplegic myocardial preservation for coronary revascularisation. *Journal of Thoracic and Cardiovascular Surgery* 1984; **88**: 174–181.
2. Akl BF, Talbot W, Neal JF, Havens D. Noncardiac operations after coronary revascularisation. *Western Journal of Medicine* 1982; **136**: 91–94.
3. Arkins R, Smessaert AA, Hicks RG. Mortality and morbidity in surgical patients with coronary artery disease. *Journal of the American Medical Association* 1964; **190**: 485–488.
4. Arous EJ, Baum PL, Cutler BS. The ischemic exercise test in patients with peripheral vascular disease. *Archives of Surgery* 1984; **119**: 780–783.
5. Backer CL, Tinker JH, Robertson DM, Vlietstra RE. Myocardial reinfarction following local anesthesia for ophthalmic surgery. *Anesthesia and Analgesia* 1980; **59**: 257–262.
6. Baer S, Nakhjavan F, Kajani M. Postoperative myocardial infarction. *Surgery, Gynecology and Obstetrics* 1965; **120**: 315–322.
7. Balderman SC, Bhayana JN, Steinbach JJ, Masud ARZ, Michalek S. Perioperative myocardial infarction: A diagnostic dilemma. *Annals of Thoracic Surgery* 1980; **30**: 370–377.
8. Bassan MM, Oatfield R, Hoffman I, Matloff J, Swan HJC. New Q waves after aortocoronary bypass surgery. *New England Journal of Medicine* 1974; **290**: 349–353.
9. Bateman TM, Matloff JM, Gray RJ. Myocardial infarction during coronary artery bypass surgery—benign event or prognostic omen? *International Journal of Cardiology* 1984; **6**: 259–263.
10. Baur HR, Peterson TA, Arnar O, Gannon PG, Gobel FL. Predictors of perioperative myocardial infarction in coronary artery operation. *Annals of Thoracic Surgery* 1980; **31**: 36–44.
11. Bedard P, Marcinek H, Morton B, Smith F, Akyurekli Y, Brais M, Keon WJ. Myocardial infarction following coronary artery bypass: Factors influencing its occurrence. *Canadian Journal of Surgery* 1977; **20**: 135–139.
12. Bernhard VM, Johnson WD, Peterson JJ. Carotid artery stenosis, association with surgery for coronary artery disease. *Archives of Surgery* 1972; **105**: 837–840.
13. Bonte FJ, Parkey RW, Graham KD, Moore J, Stokely EM. A new method for radionuclide imaging of myocardial infarcts. *Radiology* 1974; **110**: 473–474.
14. Breslow MJ, Miller CF, Parker SD, Walman AT, Rogers MC. Changes in T-wave morphology following anesthesia and surgery: A common recovery-room phenomenon. *Anesthesiology* 1986; **64**: 398–402.
15. Brindis RG, Brundage BJ, Ullyot DJ, McKay CW, Lipton MJ, Turley K. Graft patency in patients with coronary artery bypass operation complicated by perioperative myocardial infarction. *Journal of the American College of Cardiology* 1984; **3**: 55–62.
16. Brown OW, Hollier LH, Pairolero PC, Kazmier FJ, McCready RA. Abdominal aortic aneurysm and coronary artery disease. *Archives of Surgery* 1981; **116**: 1484–1487.
17. Buja LM, Parkey RW, Dees JH, Stokely EM, Harris RA, Bonte FJ, Willerson JT. Morphologic correlates of technetium-99m stannous pyrophosphate imaging of acute myocardial infarcts in dogs. *Circulation* 1975; **52**: 596–607.
18. Bulkley BH, Hutchins GM. Myocardial consequences of coronary artery bypass graft surgery. *Circulation* 1977; **56**: 906–913.
19. Butler S, Feeney N, Levine SA. Patient with heart disease as surgical risk. *Journal of the American Medical Association* 1930; **95**: 84–91.
20. Carliner NH, Fisher ML, Plotnick GD, Garbart H, Rapoport A, Kelemen MH, Moran GW, Gadacz T, Peters RW. Routine preoperative exercise testing in

patients undergoing major noncardiac surgery. *American Journal of Cardiology* 1985; **56**: 51–58.

21. Chaitman BR, Alderman EL, Sheffield LT, Tong T, Fisher L, Mock MB, Weins RD, Kaiser GC, Roitman D, Berger R, Gersch B, Schaff H, Bourassa MG, Killip T, and participating CASS medical centers. Use of survival analysis to determine the clinical significance of new Q waves after coronary bypass surgery. *Circulation* 1983; **67**: 302–309.
22. Chaitman BR, Rogers WJ, Davis K, Tyras DH, Berger R, Bourassa MG, Fisher L, Stover Hertzberg V, Judkins MP, Mock MB, Killip T. Operative risk factors in patients with left main coronary-artery disease. *New England Journal of Medicine* 1980; **303**: 953–957.
23. Chamberlain DA, Edmonds-Seal J. Effects of surgery under general anaesthesia on the electrocardiogram in ischaemic heart disease and hypertension. *British Medical Journal* 1964; **2**: 784–787.
24. Codd JE, Wiens RD, Kaiser GC, Barner HB, Tyras DH, Mudd JG, Willman VL. Late sequelae of perioperative myocardial infarction. *Annals of Thoracic Surgery* 1978; **26**: 208–214.
25. Conti VR, Bertranou EG, Blackstone EH, Kirklin JW, Digerness SB. Cold cardioplegia versus hypothermia for myocardial protection. *Journal of Thoracic and Cardiovascular Surgery* 1978; **76**: 577–588.
26. Cooperman M, Pflug B, Martin EW jr, Evans WE. Cardiovascular risk factors in patients with peripheral vascular disease. *Surgery* 1978; **84**: 505–509.
27. Crawford ES, Morris GC jr, Howell JF, Flynn WF, Moorhead DT. Operative risk in patients with previous coronary artery bypass. *Annals of Thoracic Surgery* 1978; **26**: 215–221.
28. Cruchley PM, Kaplan JA, Hug CC jr, Nagle D, Sumpter R, Finucane D. Non-cardiac surgery in patients with prior myocardial revascularisation. *Canadian Anaesthetists Society Journal* 1983; **30**: 629–634.
29. Cutler BS, Wheeler HB, Paraskos JA, Cardullo PA. Assessment of operative risk with electrocardiographic exercise testing in patients with peripheral vascular disease. *American Journal of Surgery* 1979; **137**: 484–490.
30. Deanfield JE, Selwyn AT, Chierchia S, Maseri A, Ribeiro P, Krikler S, Morgan M. Myocardial ischaemia during daily life in patients with stable angina: Its relation to symptoms and heart rate changes. *Lancet* 1983; **2**: 753–758.
31. Delva E, Maille J-G, Solymoss BC, Chabot M, Grondin CM, Bourassa MG. Evaluation of myocardial damage during coronary artery grafting with serial determinations of serum CPK MB isoenzyme. *Journal of Thoracic and Cardiovascular Surgery* 1978; **75**: 467–475.
32. Dixon SH jr, Limbird LE, Roe CR, Wager GS, Oldham HN jr, Sabiston DC jr. Recognition of postoperative acute myocardial infarction. Application of isoenzyme techniques. *Circulation* 1973; **47/48** (Suppl. 3): 137–140.
33. Domaingue CM, Davies MJ, Cronin KD. Cardiovascular risk factors in patients for vascular surgery. *Anaesthesia and Intensive Care* 1982; **10**: 324–327.
34. Driscoll AC, Hobika JH, Etsten BE, Proger S. Clinically unrecognised myocardial infarction following surgery. *New England Journal of Medicine* 1961; **264**: 633–639.
35. Edwards WH, Mulherin JL jr, Walker WE. Vascular reconstructive surgery following myocardial revascularisation. *Annals of Surgery* 1978; **187**: 653–657.
36. Eerola M, Eerola R, Kaukinen S, Kaukinen L. Risk factors in surgical patients with verified preoperative myocardial infarction. *Acta Anaesthesiologica Scandinavica* 1980; **24**: 219–223.
37. Eugene J, Ott RA, Piters KM, Stemmer EA. Operative risk factors associated with unstable angina pectoris. *Archives of Surgery* 1985; **120**: 279–282.
38. Fennell WH, Chua KG, Cohen L, Morgan J, Karunaratne HB, Resnekov L, Al-Sadir J, Lin C-Y, Lamberti JJ, Anagnostopoulos CE. Detection, prediction and significance of perioperative myocardial infarction following aorta-coronary bypass. *Journal of Thoracic and Cardiovascular Surgery* 1979; **78**: 244–253.
39. Gersh BJ, Kronmal RA, Frye RL, Schaff HV, Ryan TJ, Gosselin AJ, Kaiser GC, Killip T III, and participants in the coronary artery surgery study. Coronary arteriography and coronary artery bypass surgery: Morbidity and mortality in patients aged 65 years or older. *Circulation* 1983; **67**: 483–491.
40. Goldman L, Caldera DL, Nussbaum SR, Southwick FS, Krogstad D, Murray B, Burke DS, O'Malley TA, Goroll AH, Caplan CH, Nolan J, Carabello B, Slater EE. Multifactorial index of cardiac risk in noncardiac surgical procedures. *New England Journal of Medicine* 1977; **297**: 845–850.
41. Gray RJ, Matloff JM, Conklin CM, Ganz W, Charuzi Y, Wolfstein R, Swann HJC. Perioperative myocardial infarction: Late clinical course after coronary artery bypass surgery. *Circulation* 1982; **66**, 1185–1189.
42. Guiteras Val PG, Pelletier LC, Hernandex MG, Jais JM, Chaitman BR, Dupras G, Solymoss BC. Diagnostic criteria and prognosis of perioperative myocardial infarction following coronary bypass. *Journal of Thoracic and Cardiovascular Surgery* 1983; **86**: 878–886.
43. Hacker RW, Torka M, Golling FR, Reiss I, Schmid HJ, Stolte M. Perioperative myocardial infarction in coronary artery bypass surgery. *Thoracic and Cardiovascular Surgeon* 1980; **28**: 96–101.
44. Hertzer NR. Fatal myocardial infarction following lower extremity revascularisation. *Annals of Surgery* 1981; **193**: 492–498.
45. Hertzer NR. Fatal myocardial infarction following peripheral vascular operations. *Cleveland Clinic Quarterly* 1982; **49**: 1–11.
46. Hertzer NR. Myocardial ischemia. *Surgery* 1983; **93**: 97–101.
47. Hicks GL, Eastland MW, DeWeese JA, May AG, Rob CG. Survival improvement following aortic aneurysm resection. *Annals of Surgery* 1975; **181**: 863–869.
48. Hultgren HN, Shettigar UR, Pfeifer JF, Angell WW. Acute myocardial infarction and ischemic injury during surgery for coronary artery disease. *American Heart Journal* 1977; **94**: 146–153.
49. Hunter PR, Endrey-Walder P, Bauer GE, Stephens FO. Myocardial infarction following surgical operations. *British Medical Journal* 1968; **4**: 725–728.
50. Isom WO, Spencer FC, Feigenbaum H, Cunningham J, Roe C. Prebypass myocardial damage in patients undergoing coronary revascularisation: An unrecognised vulnerable period. *Circulation* 1975; **51/52** (Suppl. 2): 119.
51. Jeffrey CC, Kunsman J, Cullen DJ, Brewster DC. A prospective evaluation of cardiac risk index. *Anesthesiology* 1983; **58**: 462–464.
52. Källerö KS, Bergvist D, Cederholm C, Jonsson K,

Olsson P-O, Takolander R. Arteriosclerosis in popliteal artery trifurcation as a predictor for myocardial infarction after arterial reconstructive operation. *Surgery, Gynecology and Obstetrics* 1984; **159**: 133–138.

53. Kannel WB, McGee DL. Diabetes and cardiovascular risk factors: The Framingham study. *Circulation* 1979; **59**: 8–13.
54. Kannel WB, Sorlie P. Hypertension in Framingham. In: O. Paul, ed. *Epidemiology and Control of Hypertension.* Miami: Symposia Specialist, 1975; 553–593.
55. Kaplan JA, Dunbar RW. Anaesthesia for noncardiac surgery in patients with cardiac disease. In: Kaplan JA, ed. *Cardiac Anesthesia.* New York, San Francisco, London: Grune & Stratton, 1979; 377–392.
56. Kirklin JW, Conti VR, Blackstone EH. Prevention of myocardial damage during cardiac operations. *New England Journal of Medicine* 1979; **301**: 135–141.
57. Knapp RB, Topkins MJ, Artusio JR. The cerebrovascular accident and coronary occlusion in anesthesia. *Journal of the American Medical Association* 1962; **182**: 332–334.
58. Knorring J von. Postoperative myocardial infarction: A prospective study in a risk group of surgical patients. *Surgery* 1981; **90**: 55–60.
59. Levinsky L, Lajos TZ, Lee AB jr, Srinivasan V, Schimert G. Refinements in coronary artery surgery contributing to improved survival. *Thoracic and Cardiovascular Surgeon* 1980; **28**: 102–108.
60. Li W-I, Hanelin LG, Riggins RCK, Agnew RC, Annest LS, Anderson RP. Perioperative ischemic injury after coronary bypass graft surgery. *American Journal of Surgery* 1985; **150**: 122–126.
61. Lim JS, Proudfit WL, Sheldon WC, Alosilla C, Phillips DF, Loop FD. Perioperative myocardial infarction related to coronary bypass surgery. *American Heart Journal* 1978; **96**: 463–466.
62. Lowenstein E. Perianaesthetic ischemic episodes cause myocardial infarction in humans—A hypothesis confirmed. *Anesthesiology* 1985; **62**: 103–106.
63. Lowenstein E, Yusuf S, Teplick RS. Perioperative myocardial reinfarction: A glimmer of hope—A note of caution. *Anesthesiology* 1983; **59**: 493–494.
64. McAuley CE, Watson CG. Elective inguinal herniorrhaphy after myocardial infarction. *Surgery, Gynecology and Obstetrics* 1984; **159**: 36–38.
65. McCollum CH, Garcia-Rinaldi R, Graham JM, DeBakey ME. Myocardial revascularisation prior to subsequent major surgery in patients with coronary artery disease. *Surgery* 1977; **81**: 302–304.
66. McGregor CGA, Muir AL, Smith AF, Miller HC, Hannan WJ, Cameron EWJ, Wheatley DJ. Myocardial infarction related to coronary artery bypass graft surgery. *British Heart Journal* 1984; **51**: 399–406.
67. Mahar LJ, Steen PA, Tinker JH, Vleitstra RE, Smith HC, Pluth JR. Perioperative myocardial infarction in patients with coronary artery disease with and without aorta–coronary artery bypass grafts. *Journal of Thoracic and Cardiovascular Surgery* 1978; **76**: 533–537.
68. Marvin HM. The heart during anesthesia and operative procedures. *New England Journal of Medicine* 1928; **199**: 547–551.
69. Massie BM, Botvinick EH, Werner JA, Chatterjee K, Parmley WW. Myocardial scintigraphy with technetium-99m stannous pyrophosphate: An insensitive test for nontransmural myocardial infarction. *American Journal of Cardiology* 1979; **43**: 186–192.
70. Mauney FM, Ebert PA, Sabiston DC jr. Postoperative myocardial infarction: A study of predisposing factors, diagnosis and mortality in a high risk group of surgical patients. *Annals of Surgery* 1970; **172**: 497–503.
71. Miller DC, Stinson EB, Oyer PE, Jamieson SW, Mitchell RS, Reitz BA, Baumgartner WA, Shumway NE. Discriminant analysis of the changing risks of coronary artery operations: 1971–1979. *Journal of Thoracic and Cardiovascular Surgery* 1983; **85**: 197–213.
72. Nachlas MM, Abrams SJ, Goldberg MM. The influence of arteriosclerotic heart disease on surgical risk. *American Journal of Surgery* 1961; **101**: 447–455.
73. Namay DL, Hammermeister KE, Zia MS, DeRouen TA, Dodge HT, Namay K. Effect of perioperative myocardial infarction on late survival in patients undergoing coronary artery bypass surgery. *Circulation* 1982; **65**: 1066–1071.
74. Oldham HN, Roe CR, Young WG jr, Dixon SH. Intraoperative detection of myocardial damage during coronary artery surgery by plasma creatine phosphokinase isoenzyme analysis. *Surgery* 1973; **74**: 917–925.
75. Pasternak PF, Imparato AM, Bear G, Riles TS, Baumann FG, Benjamin D, Sanger J, Kramer E, Wood RP. The value of radionuclide angiography as a predictor of perioperative myocardial infarction in patients undergoing abdominal aortic aneurysm resection. *Journal of Vascular Surgery* 1984; **1**: 320–325.
76. Plumlee JE, Boettner RB. Myocardial infarction during and following anesthesia and operation. *Southern Medical Journal* 1972; **65**: 886–889.
77. Prorok JJ, Trostle D. Operative risk of general surgical procedures in patients with previous myocardial revascularisation. *Surgery, Gynecology and Obstetrics* 1984; **159**: 214–216.
78. Prys-Roberts C, Meloche R, Foëx P. Studies of anaesthesia in relation to hypertension: Cardiovascular responses of treated and untreated patients. *British Journal of Anaesthesia* 1971; **43**: 122–137.
79. Randall OS, Orr TG. Post-operative coronary occlusion. *Annals of Surgery* 1930; **92**: 1014–1018.
80. Rao TLK, Jacobs KH, El-Etr AA. Reinfarction following anesthesia in patients with myocardial infarction. *Anesthesiology* 1983; **59**: 499–505.
81. Riles TS, Kopelman I, Imparato AM. Myocardial infarction following carotid endarterectomy: A review of 683 operations. *Surgery* 1979; **85**: 249–252.
82. Rosen M, Mushin WW, Kilpatrick GS, Campbell H, Davies LGG, Harrison E. Study of myocardial ischaemia in surgical patients. *British Medical Journal* 1966; **2**: 1415–1420.
83. Sapala JA, Ponka JL, Duvernoy WFC. Operative and nonoperative risks in the cardiac patient. *Journal of the American Geriatric Society* 1975; **23**: 529–534.
84. Schaff HV, Gersh BJ, Fisher LD, Frye RL, Mock MB, Ryan TJ, Ells RB, Chaitman BR, Alderman EL, Kaiser GC, Faxon DP, Bourassa MG. Detrimental effect of perioperative myocardial infarction on late survival after coronary artery bypass. *Journal of Thoracic and Cardiovascular Surgery* 1984; **88**: 972–981.
85. Scher KS, Tice DA. Operative risk in patients with previous coronary artery bypass. *Archives of Surgery* 1976; **111**: 807–809.
86. Schneider AJL. Assessment of risk factors and surgical outcome. *Surgical Clinics of North America* 1983; **63**: 1113–1126.

87. Schneider RR, Pichard AD, Mindich B. Factors predisposing to intraoperative myocardial infarction during coronary artery bypass surgery. *Mount Sinai Journal of Medicine* 1985; **52**: 123–129.

88. Schoeppel SJ, Wilkinson C, Waters J, Meyers SN. Effects of myocardial infarction on perioperative cardiac complications. *Anesthesia and Analgesia* 1983; **62**: 493–498.

89. Skinner JF, Pearce ML. Surgical risk in the cardiac patient. *Journal of Chronic Diseases* 1964; **17**: 57–72.

90. Slogoff S, Keats AS. Does perioperative myocardial ischemia lead to postoperative myocardial infarction? *Anesthesiology* 1985; **62**: 107–114.

91. Slogoff S, Keats AS. Further observations on perioperative myocardial ischemia. *Anesthesiology* 1986; **65**: 539–542.

92. Slogoff S, Keats AS, Cooley DA, Reul GJ, Frazier OH, Ott DA, Duncan JM, Livesay JJ. Addition of papaverine to cardioplegia does not reduce myocardial necrosis. *Annals of Thoracic Surgery* 1986: **42**: 60–64.

93. Sprague HB. Heart in surgery. *Surgery, Gynecology and Obstetrics* 1929; **49**: 54–58.

94. Steen PA, Tinker JH, Tarhan S. Myocardial reinfarction after anesthesia and surgery. *Journal of the American Medical Association* 1978; **239**: 2566–2570.

95. Symes J, Allards J, Huttner I, Lisbona R, Jain A, Long R, Sniderman A. Causes of perioperative myocardial infarction: Their identification and prevention. *Canadian Journal of Surgery* 1980; **23**: 438–441.

96. Tarhan S, Moffitt EA, Taylor WF, Giuliani ER. Myocardial infarction after general anesthesia. *Journal of the American Medical Association* 1972; **220**: 1451–1454.

97. Tomatis LA, Fierens EE, Verbrugge GP. Evaluation of surgical risk in peripheral vascular disease by coronary arteriography: A series of 100 cases. *Surgery* 1972; **71**: 429–435.

98. Topkins MJ, Artusio JF. Myocardial infarction and surgery, a five year study. *Anesthesia and Analgesia* 1964; **43**: 716–720.

99. Vormittag E, Kohn P, Zekert F, Grabner H. Risikofaktoren des postoperativen myocardinfarktes. *Deutsche Medizinische Wochenscrift* 1975; **100**: 1365–1368.

100. Wells PH, Kaplan JA. Optimal management of patients with ischemic heart disease for non cardiac surgery by complementary anesthesiologist and cardiologist interaction. *American Heart Journal* 1981; **102**: 1029–1037.

101. Wilson LB. Fatal postoperative embolism. *Annals of Surgery* 1912; **56**: 809–817.

Br. J. Anaesth. (1988), **61**, 38–43

ASSESSMENT OF THE PATIENT WITH KNOWN OR SUSPECTED ISCHAEMIC HEART DISEASE FOR NON-CARDIAC SURGERY

L. GOLDMAN

When adults undergo major non-cardiac surgery, much of the potential perioperative morbidity and mortality is related to cardiac complications. Substantial recent data indicate that clinical characteristics and, in selected circumstances, additional diagnostic tests, may guide the preoperative assessment.

Routine evaluation

The history and physical examination are critical aspects of the preoperative assessment of the patient with potential ischaemic heart disease. Special care should be taken to elicit possible signs or symptoms of ischaemic heart disease and to assess the patient's functional status. Physical examination should search specifically for signs of congestive heart failure, including jugular venous distension, rales, ventricular gallops, hepatomegaly or oedema, and for signs of possible valvular heart disease. A preoperative ECG is probably indicated in all men older than 40 yr and women older than 50–55 yr, and it is definitely indicated in patients who have known or suspected heart disease based on the history and physical examination [11].

Compared with patients with no history of preoperative ischaemic heart disease, patients with angina or a previous myocardial infarction have a 10–50 fold increase in the risk of perioperative myocardial infarction. Surgery within 6 months of a preoperative myocardial infarction appears to carry a substantially higher risk than surgery that is performed more than 6 months after an infarction [14, 32, 33]. Although data from the 1970s suggested about a 30% risk of reinfarction or cardiac death with surgery within 3 months of a previous myocardial infarction and a 15% risk with surgery within 3–6 months after a previous myocardial infarction [14, 32, 33], more recent studies using invasive haemodynamic monitoring and modern anaesthetic care have reported much lower complication rates. Wells and Kaplan [35] reported on 48 patients who had surgery within 3 months after a myocardial infarction and who had no reinfarctions. Rao, Jacobs and El-Etr [28] reported a 6% rate of reinfarction for surgery within 3 months after a preoperative myocardial infarction and a 2% rate of reinfarction for surgery within 3–6 months after myocardial infarction. These data suggest that rates of reinfarction and cardiac death may be substantially lower in the 1980s than they were in the 1970s, if carefully selected patients with recent preoperative myocardial infarctions have modern monitoring and anaesthetic care.

The timing of surgery after a recent preoperative myocardial infarction requires careful consideration of the patient's functional status and of both the urgency and the likely risks and benefits of the surgical procedure. If a procedure is life-saving, it must be performed regardless of the cardiac risk. Conversely, purely elective procedures may be delayed until the patient's cardiac risk has returned to its lowest possible level, which most experts believe entails a full 6 months after the infarction.

For many patients, however, the non-cardiac surgery is neither urgently life-saving nor purely elective. In patients who have a potentially resectable malignancy or who have other serious conditions, such as severe symptomatic peripheral vascular disease, one would like to delay surgery until it is safe, but not wait a full 6 months after

---

LEE GOLDMAN, M.D., Divisions of Clinical Epidemiology and General Medicine and the Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts. Address for correspondence: Department of Medicine, Brigham and Women's Hospital, 75 Francis Street, Boston, Ma 02115, U.S.A.

the myocardial infarction. A rational approach to such patients is as follows. Scar formation after a myocardial infarction usually occurs within 4–6 weeks. At that time, the patient's functional capacity can be evaluated with studies such as a submaximal exercise tolerance test [5]. If the patient is symptomatic on minimal exercise or has major electrocardiographic changes during exercise, cardiac catheterization and subsequent consideration of revascularization is recommended. If the patient does well after the infarction and has good exercise capacity, one can consider proceeding with the non-cardiac sugery at approximately 6 weeks after the myocardial infarction. However, non-cardiac surgery should be delayed in patients who have important post-infarction angina, large reversible defects on thallium scintigraphy, marked ST-segment depression with exercise, or other evidence of severe ischaemia. Such patients should normally undergo coronary arteriography and revascularization before all but emergency surgery.

In the patient with chronic stable angina, it is vital to determine the patient's exercise tolerance in addition to the frequency of angina. Paradoxically, patients who have heart disease may report less frequent angina if their functional status declines because of serious *non-cardiac* conditions, such as orthopaedic or peripheral vascular disease [16, 17]. Thus, patients should be asked if they can perform common activities that might imply that their functional status is Class II or better, such as carrying grocery bags or any 10–15 kg object up a flight of stairs without developing appreciable symptoms or having to stop. Patients who have Class I or Class II angina using such criteria can commonly increase their heart rates and arterial pressures into the range that would be expected with well-controlled anaesthesia and surgery. Conversely, if patients cannot perform such activities because of symptoms of ischaemic heart disease, further evaluation is warranted.

In selecting tests for further evaluation, special attention must be given to the patient's particular characteristics. Exercise treadmill testing can assess both the patient's exercise tolerance and also his/her probability of ischaemic heart disease. Although exercise tests are not perfectly accurate for diagnosing the presence or absence of ischaemic heart disease, they are extremely useful for assessing functional status. Thus, patients who can perform at least five metabolic equivalents of exercise appear less likely to develop postoperative death or myocardial infarction than patients who cannot [3], and patients older than 65 yr who cannot perform 2 min of supine bicycle exercise and raise their heart rates above 99 beat min^{-1} also appear to be at higher risk (table I) [10].

Poor left ventricular function, as demonstrated by either echocardiography or radionuclide ventriculography, can identify patients who are at higher risk of complications. However, such tests at rest do not provide functional information and may not identify patients in whom potential interventions are likely to change risk.

The most difficult clinical subset are those patients who are unable to exercise because of non-cardiac conditions such as peripheral vascular disease or orthopaedic conditions. In such patients, dipyridamole–thallium imaging is potentially useful (table II) [1, 20, 24]. The highest risk group appears to be patients who have underlying symptoms and who also have reversible defects on thallium imaging (table III) [8]. The principal limitation of dipyridamole–thallium imaging is that it demonstrates anatomical abnormalities without necessarily giving a clear indication of the physiological severity. If a physiological test is needed, right atrial pacing can be combined with thallium imaging and haemodynamic measurements to assess the patient's response to tachycardia [18]. Despite its limitations, dipy-

TABLE I. *Risk stratification for major abdominal or non-cardiac thoracic surgery in patients older than 65 yr [10]*

	No. patients	No. compli-cations	No. deaths
"Goldman Indicator"			
Present	59	16	6
Absent			
Unable to exercise to HR > 99 beat min^{-1}	31	6	2
Able to exercise to HR > 99 beat min^{-1}	66	1	0

TABLE II. *Dipyridamole–thallium scanning in vascular surgery patients [1, 24]*

Reversible thallium defect	No. patients	No. MI or death
Present	58	15 (26%)
Absent	76	1 (1.3%)
Total	134	16 (12%)

TABLE III. *Value of dipyridamole–thallium scanning in different clinical subgroups* [8]

History of MI, angina, CHF, or diabetes, or Q wave on ECG	No. patients	No. ischaemic events
Yes		
Reversible thallium defect present	33	15
Reversible thallium defect absent	26	2
No		
Reversible thallium defect present	9	1
Reversible thallium defect absent	43	0

ridamole–thallium imaging appears to be a potentially useful way to evaluate patients in whom other non-invasive tests are not helpful.

Ambulatory ischaemia monitoring is another potential means for detecting ischaemia in patients who are unable to exercise. Early data suggest that patients who have ischaemia on monitoring are more likely to have cardiac events during follow-up [29], but it is too early to know the precise role for ambulatory monitoring in selecting patients for surgery.

Cardiac catheterization is indicated before all but truly emergency surgery in patients who would normally be candidates for coronary artery bypass grafting based on the severity of their symptoms. Coronary angiography should also be considered in patients who are identified as having Class III or more severe angina during the preoperative evaluation, and in symptomatic patients who have markedly positive exercise treadmill tests, transient defects on dipyridamole–thallium scanning, or who are at high risk because of recent myocardial infarctions or other combinations or risk factors (see Multifactorial Assessment of Risk).

Patients who have had previous coronary revascularization can undergo subsequent non-cardiac surgery with low mortality rates [19, 22, 25], except perhaps in the first 30 days after the revascularization [4]. In the Coronary Artery Surgery Study Registry of patients who had mild stable angina or who were asymptomatic after a myocardial infarction [9], total operative mortality for major non-cardiac surgery was 0.9% in patients who had coronary revascularization before the non-cardiac surgery and 2.4% among patients who had the major non-cardiac surgery without preceding coronary artery surgery. However, if one considers the average 1.4% mortality from the coronary revascularization, the total mortality in the two groups was similar. Furthermore, the risk of perioperative myocardial infarction at the time of the non-cardiac surgery was not different in the two groups.

Although early investigators expressed concern on the safety of anti-anginal medications, especially beta-blockers, in the perioperative period, subsequent data have emphasized the safety of continuing such medications and the dangers of sudden discontinuation [2, 12, 23]. Beta-blockers diminish the risk of severe hypertension or ischaemia during intubation, anaesthesia and surgery [26, 27]. In general, anti-anginal medication should be continued up to and often including the morning of surgery and recommenced as soon as possible after operation. For patients with important angina, propranolol can be given i.v. according to several well-documented regimens [31, 36]. Since beta-blockers, even propranolol, have a tissue half-life of approx. 24 h, i.v. medications should not be required in the operating theatre and usually need not be started until at least a day after they have been discontinued orally.

There are no convincing data to indicate any major clinical cardiac complications from the use of calcium channel antagonists in the perioperative period. Nifedipine may be given sublingually, and nitrates may be give sublingually,

TABLE IV. *Multifactorial Index of Cardiac Risk in non-cardiac surgery* [13]. †*Defined as:* $P_{O_2} < 8$ *kPa;* $P_{CO_2} > 6.7$ *kPa;* $K^+ < 3.0$ *mmol litre*$^{-1}$*;* $HCO_3^- < 20$ *mmol litre*$^{-1}$*; blood urea* > 18 *mmol litre*$^{-1}$*; creatinine* > 260 *mmol litre*$^{-1}$*; abnormal SGOT; signs of chronic liver disease; bed-ridden from non-cardiac causes. APB = atrial premature beat*

	Points
History	
Myocardial infarction within 6 months	10
Age > 70 yr	5
Physical examination	
S-3 or jugular venous distension	11
Important aortic stenosis	3
Electrocardiogram	
Rhythm other than sinus or sinus plus APB on last preoperative electrocardiogram	7
More than five premature ventricular beats per minute at any time before operation	7
Poor general medical status†	3
Intraperitoneal, intrathoracic or aortic surgery	3
Emergency operation	4
Total	53

topically or i.v. to aid in the management of intraoperative or postoperative ischaemia.

Intraoperative monitoring

In patients with severe heart disease, careful intraoperative monitoring, including intraarterial pressure recordings and pulmonary artery catheterization, appear to be helpful [35, 28]. It is difficult at this time, however, to establish definitive guidelines as to exactly which patients should receive such invasive monitoring. Nevertheless, more aggressive intraoperative procedures have been associated with lower risks of perioperative myocardial infarction [35, 28]. Thus, a major area for future investigation will be to determine which type of patients are likely to have a cost-effective benefit from such expensive and invasive monitoring techniques.

TABLE V. *Modified Multifactorial Index* [7]. *APB = atrial premature beat. †As defined in table IV*

	Points
Coronary artery disease	
Myocardial infarction within 6 months	10
Myocardial infarction more than 6 months	5
Canadian Cardiovascular Society angina	
Class III	10
Class IV	20
Unstable angina within 6 months	10
Alveolar pulmonary oedema	
Within 1 week	10
Ever	5
Valvular disease	
Suspected critical aortic stenosis	20
Arrhythmias	
Rhythm other than sinus or sinus plus APB on last preoperative electrocardiogram	5
More than five premature ventricular contractions at any time before surgery	5
Poor general medical status†	5
Age > 70 yr	5
Emergency operation	10

Multifactorial assessment of risk

My colleagues and I have previously reported on a multifactorial index that incorporates several pieces of information from the history, physical examination and laboratory to estimate a patient's overall risk of major cardiac complications (table IV) [13]. More recently, a revised version of the original index was proposed and shown to be equally good when evaluated in one institution (table V) [6, 7]. The original multifactorial index (table IV) has been evaluated more widely [7, 10, 21, 22, 34, 37], and it appears able to provide prognostic stratification in a wide variety of settings (table VI). By considering three different types of patient and planned surgical procedures, a patient's score on the multifactorial index can be integrated with this information to provide a well-validated likelihood of major cardiac complications (table VII).

Type of anaesthesia

There are currently no data to document that the choice of the type of anaesthesia is a major correlate of perioperative clinical cardiac complications. There appears to be no benefit from spinal compared with general anaesthesia, probably because unplanned intraoperative hypotension is as likely with spinal anaesthesia as with general anaesthesia.

TABLE VI. *Major complication rates in four studies that have analysed the Multifactorial Cardiac Risk Index*[13]. *Complications include documented myocardial infarction, cardiogenic pulmonary oedema, ventricular tachycardia, or cardiac death. *Actual unpublished numbers provided by Dr Detsky. † Sensitivity ÷ (1-specificity)*

	Goldman et al.[14]	Zeldin[37]	Detsky et al.[7]	Jeffrey et al.[21]		
Type of patient	Unselected non-cardiac surgery > 40 yr	Unselected non-cardiac surgery > 40 yr	Preoperative medical consultations	Abdominal aortic aneurysm surgery	Pooled	Pooled Likelihood Ratio†
Overall complication rate	58/1001 (6%)	35/1140 (3%)	27/268 (10%)	11/99 (11%)	131/2508 (5.2%)	
Complication rate by class						
Class I (0–5 points)	5/537 (1%)	4/590 (1%)	8/134 (6%)	4/56 (7%)	21/1317 (1.6%)	0.29
Class II (6–12 points)	21/316 (7%)	13/453 (3%)	6/85 (7%)	4/35 (11%)	44/889 (5%)	0.94
Class III (13–25 points)	18/130 (14%)	11/74 (15%)	9/45 (20%)	3/8 (38%)	41/257 (16%)	3.4
Class IV (⩾ 26 points)	14/18 (78%)	7/23 (30%)	4/4 (100%)	0	25/45 (56%)	22.7

TABLE VII. *Use of the Multifactorial Cardiac Risk Index to estimate the probability of cardiac complications in different types of patients [13]. *Calculated by multiplying the prior odds of complications by the likelihood ratio for each class*

Type of patient	Approximate baseline risk of major cardiac complications for this type of patient (%)	Approximate risk of major cardiac complications in this type of patient as adjusted using Multifactorial Index (%)*			
		Class I	Class II	Class III	Class IV
Minor surgery	1	0.3	1	3	19
Unselected consecutive patients older than 40 yr who have major non-cardiac surgery	4	1.2	4	12	48
Patients who have abdominal aortic aneurysm surgery or who are older than 40 yr and have high risk characteristics that generally generate medical consultations before major non-cardiac surgery	10	3	10	30	75

Postoperative considerations

Studies from the 1970s consistently showed that most postoperative myocardial infarctions occurred within 6 days after surgery, with a peak around the 3rd day after operation [30]. More recent preliminary data, however, suggest that many smaller non-Q wave infarctions may occur much earlier during the postoperative period and may be detectable by continuous electrocardiographic monitoring and frequent sampling of creatine kinase isoenzymes. At least 50% of postoperative myocardial infarctions are painless, and many such infarctions present with otherwise unexplained alterations in vital signs or mental status [15, 30].

SUMMARY

The perioperative care of the patient with known or suspected ischaemic heart disease requires careful co-ordination among the anaesthetist, surgeon and medical consultant. Careful preoperative evaluation can aid the identification of risk, the selection of preoperative interventions that may reduce risk, and decisions on intraoperative and postoperative monitoring. Although uncontrolled observational data suggest that such careful management allows for improved outcome, more carefully controlled studies are required to determine the precise benefits and cost-effectiveness of many of the expensive and often invasive interventions that are currently available.

REFERENCES

1. Boucher CA, Brewster DC, Darling RC, Okada RD, Strauss HW, Pohost GM. Determination of cardiac risk by dipyridamole–thallium imaging before peripheral vascular surgery. *New England Journal of Medicine* 1985; 312: 389–394.
2. Caralps JM, Mulet J, Wienke HR, Moran JM, Pifarre R. Results of coronary artery surgery in patients receiving propranolol. *Journal of Thoracic and Cardiovascular Surgery* 1974; 67: 526–529.
3. Carliner NH, Fisher ML, Plotnick GD, Garbart H, Rapoport A, Kelemen MH, Moran GW, Gadacz T, Peters RW. Routine preoperative exercise testing in patients undergoing major noncardiac surgery. *American Journal of Cardiology* 1985; 56: 51–58.
4. Crawford ES, Morris GC, Howell JF, Flynn WF, Moorhead DT. Operative risk in patients with previous coronary artery bypass. *Annals of Thoracic Surgery* 1978; 26: 215–221.
5. DeBusk RF, Kraemer HC, Nash E, Berger WE, Lew H. Stepwise risk stratification soon after acute myocardial infarction. *American Journal of Cardiology* 1983; 52: 1161–1166.
6. Detsky AS, Abrams HB, Forbath N, Scott JG, Hilliard JR. Cardiac assessment for patients undergoing noncardiac surgery. A multi-factorial clinical risk index. *Archives of Internal Medicine* 1986; 146: 2131–2134.
7. Detsky AS, Abrams HB, McLaughlin JR, Drucker DJ, Sasson Z, Johnston N, Scott JG, Forbath N, Hilliard JR. Predicting cardiac complications in patients undergoing non-cardiac surgery. *Journal of General Internal Medicine* 1986; 1: 211–219.
8. Eagle KA, Singer DE, Brewster DC, Darling RC, Mulley AG, Boucher CA. Dipyridamole–thallium scanning in patients undergoing vascular surgery. Optimizing preoperative evaluation of cardiac risk. *Journal of the American Medical Association* 1987; 257: 2185–2189.
9. Foster ED, Davis KB, Carpenter JA, Abele S, Fray D, and Principal Investigators of CASS and Their Associates. Risk of noncardiac operation in patients with defined coronary disease. The Coronary Artery Surgery

Study (CASS) registry experience. *Annals of Thoracic Surgery* 1986; **41**: 42–50.

10. Gerson MC, Hurst JM, Hertzberg VS, Doogan PA, Cochran MB, Lim SP, McCall N, Adolph RJ. Cardiac prognosis in noncardiac geriatric surgery. *Annals of Internal Medicine* 1985; **103**: 832–837.
11. Goldberger AL, O'Konski M. Utility of the routine electrocardiogram before surgery and on general hospital admission. Critical review and new guidelines. *Annals of Internal Medicine* 1986; **105**: 552–557.
12. Goldman L. Noncardiac surgery in patients receiving propranolol. Case reports and a recommended approach. *Archives of Internal Medicine* 1981; **141**: 193–196.
13. Goldman L. Multifactorial index of cardiac risk in noncardiac surgery—a 10 year status report. *Journal of Cardiothoracic Anesthesia* 1987; **1**: 237–244.
14. Goldman L, Caldera DL, Nussbaum SR, Southwick FS, Krogstad D, Murray B, Burke DS, O'Malley TA, Goroll AH, Caplan CH, Nolan J, Carabello B, Slater EE. Multifactorial index of cardiac risk in non-cardiac surgical procedures. *New England Journal of Medicine* 1977; **297**: 845–850.
15. Goldman L, Caldera DL, Southwick FS, Nussbaum SR, Murray B, O'Malley TA, Goroll AH, Caplan CH, Nolan J, Burke DS, Krogstad D, Carabello B, Slater EE. Cardiac risk factors and complications in non-cardiac surgery. *Medicine (Baltimore)* 1978; **47**: 357–370.
16. Goldman L, Cook EF, Mitchell N, Flatley M, Sherman H, Cohn PF. Pitfalls in the serial assessment of cardiac functional status. *Journal of Chronic Disease* 1982; **35**: 763–771.
17. Goldman L, Hashimoto B, Cook EF, Loscalzo A. Comparative reproducibility and validity of systems for assessing cardiovascular functional class. Advantages of a new Specific Activity Scale. *Circulation* 1981; **64**: 1227–1234.
18. Heller GV, Aroesty JM, Parker JA, McKay RG, Silverman KJ, Als AV, Come PC, Kolodny GM, Grossman W. The pacing stress test: Thallium-201 myocardial imaging after atrial pacing: diagnostic value in detecting coronary disease compared with exercise testing. *Journal of American College of Cardiology* 1984; **3**: 1197–1204.
19. Hertzer NR, Young JR, Kramer JR, Phillips DF, deWolfe VG, Ruschhaupt WF, Beven EG. Routine coronary angiography prior to elective aortic reconstruction: results of selective myocardial revascularization in patients with peripheral vascular disease. *Archives of Surgery* 1979; **114**: 1336–1344.
20. Homma S, Callahan RJ, Ameer B, McKusick KA, Strauss HW, Okada RD, Boucher CA. Usefulness of oral dipyridamole suspension for stress thallium imaging without exercise in the detection of coronary artery disease. *American Journal of Cardiology* 1986; **57**: 503–508.
21. Jeffrey CC, Kunsman J, Cullen DJ, Brewster DC. A prospective evaluation of cardiac risk index. *Anesthesiology* 1983; **58**: 462–464.
22. Kaplan JA, Dunbar RW. Anaesthesia for noncardiac surgery in patients with cardiac disease. In: Kaplan JA, ed. *Cardiac Anesthesia*. Orlando: Grune & Stratton, 1979; 377–392.
23. Kaplan JA, Dunbar RW, Bland JW, Sumpter R, Jones EL. Propanolol and cardiac surgery. A problem for the anesthesiologist. *Anesthesia and Analgesia* 1975; **54**: 571–572.
24. Leppo J, Plaja J, Gionet M, Tumolo J, Paraskos JA, Cutler BS. Non-invasive evaluation of cardiac risk before elective vascular surgery. *Journal of the American College of Cardiology* 1987; **9**: 269–276.
25. Mahar LJ, Steen PA, Tinker JA, Vlietstra RE, Smith HC, Pluth JR. Perioperative myocardial infarction in patients with coronary artery disease with and without aorta–coronary bypass grafts. *Journal of Thoracic and Cardiovascular Surgery* 1978; **76**: 533–537.
26. Prys-Roberts C. Hemodynamic effect of anaesthesia and surgery in renal hypertensive patients receiving large doses of beta-receptor antagonists. *Anesthesiology* 1979; 51 (Suppl.): 122.
27. Prys-Roberts C, Foëx P, Roberts JG. Studies of anaesthesia in relation to hypertension. *British Journal of Anaesthesia* 1973; **45**: 671–680.
28. Rao TLK, Jacobs KH, El-Etr AA. Reinfarction following anesthesia in patients with myocardial infarction. *Anesthesiology* 1983; **59**: 499–505.
29. Rocco MB, Nable EG, Campbell S, Goldman L, Barry J, Mead K, Selwyn AP. Prognostic importance of myocardial ischemia detected by ambulatory monitoring in patients with coronary disease. *Journal of the American College of Cardiology* 1987; **9** (Suppl.A): 68A.
30. Salem DN, Homans DC, Isner JM. Management of cardiac disease in the general surgical patient. In Harvey WP, ed. *Current Problems in Cardiology*, Vol. 5. Chicago: Year Book Medical Publishers, 1980; 1–41.
31. Smulyan H, Weinberg SE, Howanitz PJ. Continuous propranolol infusion following abdominal surgery. *Journal of the American Medical Association* 1982; **247**: 2539–2542.
32. Steen PA, Tinker JH, Tarhan S. Myocardial reinfarction after anesthesia and surgery. *Journal of the American Medical Association* 1978; **239**: 2566–2570.
33. Tarhan S, Moffitt EA, Taylor WF, Guilioni ER. Myocardial infarction after general anesthesia. *Journal of the American Medical Association* 1972; **220**: 1451–1454.
34. Weathers LW, Paine R. The risk of surgery in cardiac patients. *Internal Medicine* 1981; **2**: 57–64.
35. Wells PH, Kaplan JA. Optimal management of patients with ischemic heart disease for noncardiac surgery by complementary anesthesiologist and cardiologist interaction. *American Heart Journal* 1981; **102**: 1029–1037.
36. Woolsey RL, Shand DG. Pharmacokinetics of antiarrhythmic drugs. *American Journal of Cardiology* 1978; **41**: 986–995.
37. Zeldin RA. Assessing cardiac risk in patients who undergo noncardiac surgical procedures. *Canadian Journal of Surgery* 1984; **27**: 402–404.

Br. J. Anaesth. (1988), **61**, 44–55

EXPERIMENTAL MODELS OF MYOCARDIAL ISCHAEMIA

P. FOËX

Our current understanding of the mechanisms of myocardial ischaemia and most of our knowledge of the effects of drugs on the ischaemic myocardium rest on studies based on experimental models ranging from the isolated heart muscle to the intact heart. In this review, the characteristics of the most commonly described models will be discussed. This will be illustrated by examples relevant to coronary artery disease and anaesthesia.

Isolated Heart Muscle Preparation

Strips of atrial or ventricular muscle, or papillary heart muscles, constitute the simplest model used to test the effects of interventions on the heart. The strips of heart muscle are placed in an oxygenated physiological solution within seconds of their removal in order to maintain their viability. Attachment to force or length transducers, or to both, makes it possible to measure force, length and velocity of contraction under completely controlled conditions of rate of stimulation and environment (fig. 1, table I). Neural, hormonal and humoral interferences are excluded. Moreover, the initial fibre length (the preload), and the force to be overcome before the muscle may shorten (the afterload), can be accurately controlled and, when necessary, modified during contraction (quick-release technique [23]). Experiments fall into three categories: isometric (force is developed but the muscle may not shorten), isotonic (the afterload is predetermined, the muscle will be able to shorten), and quick-release contractions (the afterload is varied during contraction).

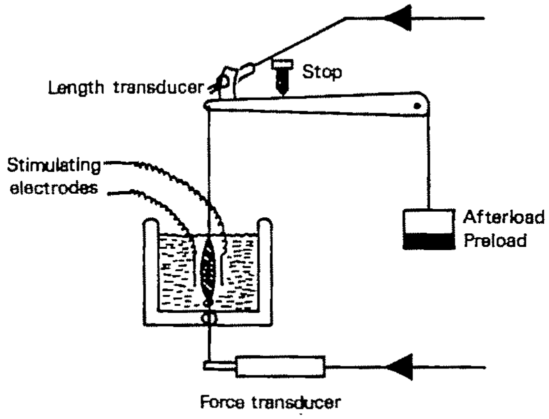


FIG. 1. Diagrammatic representation of an isolated heart muscle preparation. The muscle is attached to a force transducer and to a length transducer (here a photoelectric cell measures the light absorption of a graduated film attached to the lever).

TABLE I. *Isolated heart preparations*

Complete control of:	Rate of stimulation Preload Afterload Environment
Complete description of:	Force development Instantaneous length Instantaneous velocity

Most of our current knowledge of cardiac mechanics is based on the analysis of the behaviour of such isolated heart muscle preparations. The instantaneous relationships between force, length, velocity and time provide insights into differences between changes in the inotropic state of the myocardium, modifications caused by changes in the rate of stimulation (Bowditch staircase phenomenon), preload (Starling's law of the heart), and afterload [11]. While early studies were concerned mostly with systolic function, recent studies have elucidated many features of diastolic function [12]. This is particularly important because ischaemia alters diastolic function before it begins to depress systolic function. With such models the effects of ischaemia proper cannot be studied because the preparation is immersed in a bath and not perfused. However, the effects of hypoxia can be investigated. By reducing the oxygen concentration, while main-

---

P. FOËX, M.A., D.PHIL., F.F.A.R.C.S., Nuffield Department of Anaesthetics, Radcliffe Infirmary, Woodstock Road, Oxford OX1 6HE.

taining the carbon dioxide concentration constant, it can be shown that performance of the isolated heart muscle declines as the oxygen concentration is reduced. It can also be shown that relaxation is impaired by hypoxia. This impairment, measured as a reduced rate of relaxation, is a feature not only of hypoxia, but also of reoxygenation. Indeed, with reoxygenation the time to peak tension and the rate of relaxation can be substantially prolonged even though the amplitude of contraction has recovered [72]. The impairment of relaxation during reoxygenation is substantially attenuated by nifedipine [14].

In heart muscle preparations, oxygenation is exclusively by diffusion and, depending upon the diameter of the strips of heart muscle used, mechanical activity can be maintained only in the presence of high oxygen concentrations. This has made it difficult to assess the effect of nitrous oxide on contractility. As oxygen is replaced by nitrous oxide, the observed effects may result from both relative hypoxia and nitrous oxide [31]. The only way to avoid this problem is to study preparations that can tolerate oxygen concentrations of approximately 50%. It is then possible to examine the effect of concentrations of nitrous oxide, up to 50%, in the presence of 50% oxygen: nitrous oxide decreases contractility and impairs relaxation in a dose-dependent fashion [59].

During severe hypoxia cardiac muscle must rely on anaerobic metabolism to maintain function, thus an increased glucose concentration may be advantageous. Indeed, Apstein, Bing and Levine [2] have shown that glucose 22 mmol litre^{-1} improved tension development during hypoxia, while beta-adrenergic stimulation with isoprenaline caused a transient improvement followed by mechanical deterioration and poor recovery after re-oxygenation.

Besides the high concentrations of oxygen required to maintain adequate function, isolated heart muscle preparations operate under constant conditions of carbon dioxide exchange (the concentration of carbon dioxide in the bath being controlled), ionic diffusion gradients and diffusion of by-products of cellular metabolism. While true ischaemia in the intact heart impairs "clearance" of metabolites from the ischaemic myocardium, hypoxia in isolated heart preparations does not.

Implications of hypoxia

The mechanical performance of the heart is depressed by hypoxia; activation is still achieved in the early phase of contraction, but the velocity and extent of shortening are depressed at any given load. Indeed, both velocity and extent of shortening are more sensitive to loading during hypoxia than in normoxia. The mechanism of reduced contractility may involve a reduction in the amount of calcium delivered to the active sites, or a decrease in the sensitivity of active sites to calcium. Duration of contraction and relaxation is prolonged. This appears to be independent of endogenous catecholamines, suggesting that calcium sequestration is impaired [37]. That alterations in cardiac muscle relaxation are the result of modified active processes, rather than a simple change in the viscoelastic properties of the myocardium, has been shown in studies involving passive stretching of papillary heart muscle. The module of distensibility of papillary muscles was not significantly altered by hypoxia [48].

Isolated Ventricle

While studies of isolated strips of cardiac muscle have provided much information on the determinants of contraction and relaxation, their application to the intact heart may not be fully justified because of the complexity of the geometry of the intact ventricle [41]. However, in the intact heart it is difficult to control ventricular pressure and measure absolute ventricular volume. Closed-loop servo systems have been developed which allow venticular volume to be controlled and isotonic contraction to be obtained. Such models require coronary perfusion through an oxygenator or via a donor animal. An electro–hydraulic activator coupled to a piston connected to an intraventricular balloon is controlled by a servo logic control unit, so that during diastole the intraventricular volume increases and during systole the volume decreases at a rate appropriate to maintain ventricular pressure at a preset level. As pressure and volume are accurately set and determined, left ventricular performance can be quantified as accurately as in the isolated heart muscle [41]. With such models it has been shown that oxygen consumption is related to the force–time integrals over systole, and is increased when large rapid ejections are allowed to occur early in systole. This pattern of oxygen consumption may explain why moderate ischaemia does not cause marked reductions in systolic pressure and shortening. Although the oxygen supply is limited, there is enough oxygen in the early stage of systole for mechanical activity to be almost normal.

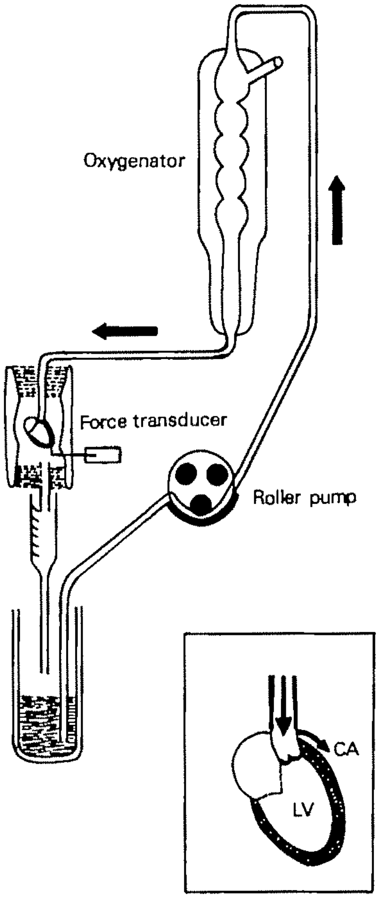


FIG. 2. Diagrammatic representation of Langendorff's preparation. Perfusion of the heart is retrograde (indicated by arrows in the insert). LV = left ventricle; CA = coronary arteries. Note that the ventricle is empty.

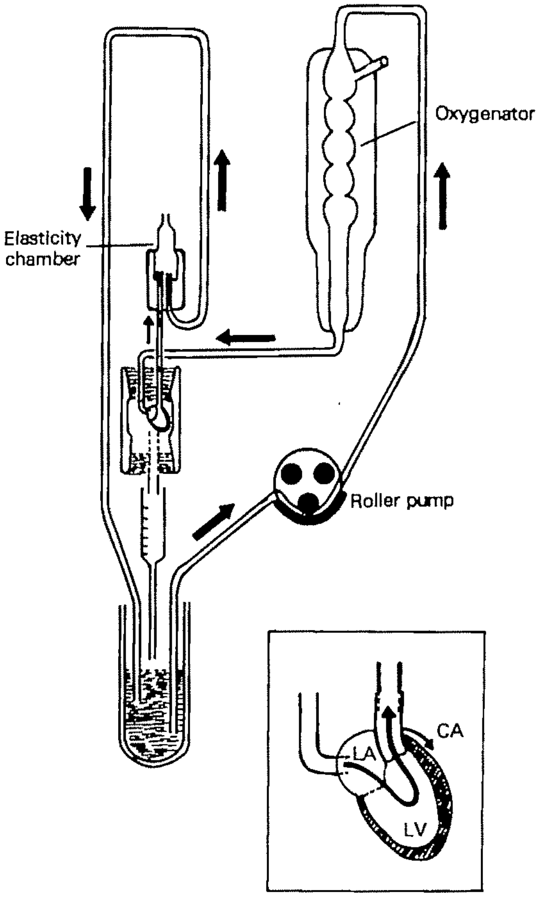


FIG. 3. Diagrammatic representation of the working isolated heart. The main differences with Langendorff's preparation is the elasticity chamber into which the left ventricle ejects, and the anterograde perfusion via the left atrium (see arrows in insert). LA = left atrium; LV = left ventricle, CA = coronary arteries.

However, as the available oxygen has been used up by systole, marked abnormalities of left ventricular relaxation occur. Eventually, with severe ischaemia, even the early phase of systole becomes abnormal [21, 71, 74].

Isolated Heart Preparations

The isolated perfused heart has been widely used to study myocardial metabolism, and to investigate the effects of hypoxia and ischaemia. Two types of preparation have gained widespread popularity: the Langendorff preparation (fig. 2) and the working heart preparation (fig. 3). Hearts from small mammals (cat, mouse, guineapig, rabbit, rat) are perfused with a buffered solution (usually Krebs–Henseleit bicarbonate buffer) to which a metabolic substrate (generally glucose) is added. The solution is equilibrated with a gas mixture containing 5% carbon dioxide in oxygen. High oxygen concentrations and high coronary flow rates are required to ensure adequate oxygen supply in the absence of red cells. These preparations are denervated, beat spontaneously at rates within the physiological range, and can be paced to a constant rate. Some of their characteristics, however, differ substantially (table II).

The Langendorff preparation

The heart is rapidly removed and cooled to 4–10 °C to cause hypothermic arrest. Cannulation of the aorta allows the warmed perfusion fluid (37 °C) to flow in a retrograde fashion down the aorta and into the coronary arteries. The perfusion pressure being at 50–100 cm H_2O, the aortic

TABLE II. *Comparison of Langendorff and Neely preparations*

Langendorff	Neely
Beating heart	Beating heart
No flow generated	Measurable flow generated
Low oxygen consumption	Normal oxygen consumption
High coronary flow	Very high coronary flow

valve remains closed, ensuring a coronary flow 5–12 ml min^{-1}/g of wet weight. The perfusion fluid traverses the coronary vascular bed, enters the right heart, and is ejected through the pulmonary artery. This preparation constitutes a beating heart which does not perform any work, since the left ventricle is empty; thus its oxygen consumption is much lower than that of working heart [22, 44].

The working heart preparation (Neely)

The heart is initially prepared in the same way as for a Langendorff preparation. It is then allowed to stabilize before being converted to a working preparation [55] by transferring perfusion from the aorta to the left atrium (the atrial reservoir being 15–20 cm above the heart). The left ventricle ejects via the aortic cannula into a bubble trap/elasticity chamber, against a hydrostatic pressure head usually set at 100 cm H_2O. The coronary arteries are perfused during both ventricular ejection and diastole (back-flow), and the coronary effluent is ejected via the pulmonary artery into the glass chamber that houses the heart, and can be collected. With this type of working heart, myocardial oxygen consumption is in the normal range while coronary blood flow is high (15–25 ml min^{-1} g^{-1} compared with 3 ml min^{-1} g^{-1} for the perfused rat heart) because of the lack of red cells in the perfusate [70].

Ischaemia or hypoxia

Both the Langendorff and the working heart preparations can be used to study the effects of hypoxia on the heart, simply by replacing some of the oxygen with nitrogen in the gassing mixture [36].

In Langendorff preparations ischaemia can be induced by reducing the coronary flow by perfusing the heart through an adjustable peristaltic pump, or by reducing the perfusion pressure. In the working heart preparation, such simple methods of controlling coronary blood flow are not available because the inflow to the left atrium corresponds to the total heart output. The introduction of a one-way valve just distal to the coronary orifices prevents diastolic back-flow and this leads to the development of ischaemia, because flow can occur only during systole. With both types of preparations regional ischaemia may be studied by ligating coronary arteries.

Ischaemia and hypoxia differ in that ischaemia is caused by a reduction of coronary flow (or an imbalance between oxygen supply and demand) which implies not only inadequate oxygen supply, but also inadequate supply of substrates, and reduced clearance of metabolic by-products (including carbon dioxide), leading to cellular acidosis. With hypoxia, coronary flow is maintained or increased (because of the lower coronary vascular resistance), and substrate supply and removal of metabolic by-products (including carbon dioxide) are increased. This minimizes the severity of cellular acidosis. Comparisons of studies of hypoxia and ischaemia make it possible to examine the relative role of oxygen lack, substrate deficiency and impaired handling of metabolic by-products.

The introduction of nuclear magnetic resonance allows the level of high energy phosphates in isolated heart preparations to be measured while they are beating. Changes in oxygenation (hypoxia or ischaemia) can be imposed in a reversible manner, and the resulting alterations in high energy phosphates and intramyocardial pH quantified. Occlusion of the left anterior descending coronary artery causes a rapid decrease in intracellular phosphocreatine and adenosine triphosphate concentrations, while intracellular pH decreases to about 5.8 [51]. Previously, high energy phosphates could be measured only after rapid freezing of the heart.

Using voltage-sensitive merocyanine dyes it is possible to monitor optically, changes in transmembrane potential in the working heart preparation. Fluorescence action potentials can be measured in a large number of sites in order to obtain detailed spatial and temporal measurements of the epicardial electrical activity [64]. NADH may also be measured by fluorimetry, thus making it possible to study simultaneously alterations in action potentials and cellular metabolism. Anoxic episodes cause conduction delays across the atrio–ventricular (AV) node and decrease the action potential duration (possibly as a result of the changes in heart rate), and finally cause complete AV nodal block. NADH fluorescence increases very rapidly after anoxia has begun and returns to normal, provided oxygenation is restored within 10 min.

Sarcolemmal Na^+–K^+-ATPase may be significantly reduced by ischaemia and reperfusion. These effects may be prevented by oxygen-radical scavengers (superoxide dismutase, catalase, etc.) suggesting that oxygen-radicals play an important role in the reduction of Na^+–K^+-ATPase and sodium pump activities [43].

The oxygen-radical scavengers may prevent the lipid peroxidation of sarcolemmal membranes, and thus protect the sodium pump, when added to the perfusion fluid of Langendorff preparations.

One of the major challenges in cardiology is to determine biochemical or pharmacological interventions that may reduce or delay the onset of ischaemic damage. Using Langendorff preparations, Nayler, Ferrari and Williams [54] have been able to show that isolated heart preparations exhibit lower myoplasmic Ca^{2+} concentrations, recover their high energy phosphates more rapidly, and exhibit stronger post-ischaemic mechanical activity when calcium antagonists have been given before the ischaemic insult. Similarly, de Leiris, Harding and Pestre [45] have shown, in working heart preparations, that pretreatment with a calcium antagonist enhances the recovery of cardiac work, creatine phosphate and total adenosine nucleotides, while reducing lactate output and LDH release. Such studies, together with many others, have contributed to the wide use of calcium antagonists in ischaemic heart disease.

Protection of the myocardium against the effects of acute coronary occlusion has been demonstrated (autofluorescence photography) for hyaluronidase and methylprednisolone, but not propranolol, in this type of preparation [76].

Differences in carbohydrate utilization between anoxia and ischaemia, are quite obvious. Ischaemic tissue has a glycolytic rate that is much lower than that of anoxic hearts [63]; in the absence of insulin, tissue lactate accumulates 10-fold during 20 min of ischaemia, as opposed to only threefold in anoxic tissue. An important observation in this model was that insulin worsened tissue lactate during ischaemia, while reducing it in anoxia. This confirmed the marked differences that exist between ischaemia and anoxia; conclusions based on observations made in anoxia may not be extrapolated to ischaemia.

Cardiac Bypass Preparations

While isolated heart muscle and isolated heart preparations can be used under completely controlled conditions, the intact heart is necessarily subjected to neural, hormonal and humoral influences, and to the effects of alterations of both the peripheral and pulmonary circulations. By using a variety of cardiac bypass preparations, control of some of the variables can be obtained (fig. 4). Important physiological data regarding the intact left ventricle, connected to a normal vascular bed, can be obtained using right heart bypass preparations. This removes the influence of right ventricular function, and of the pulmonary circulation, on the left heart. Inter-

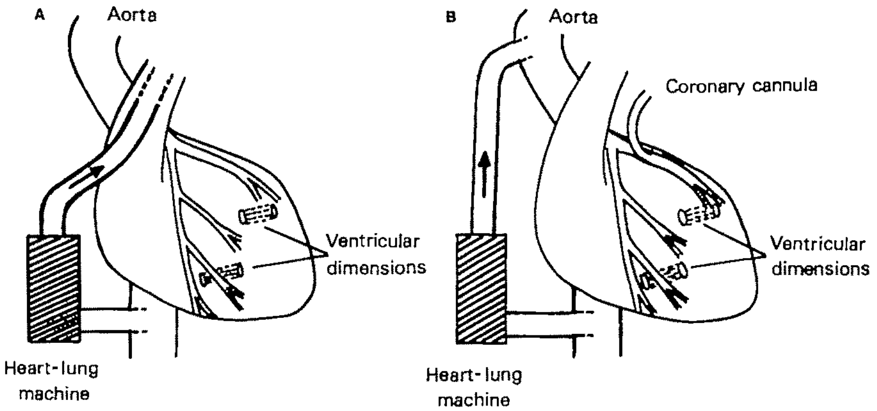


FIG. 4. Example of bypass preparations of either right (A) or right and left ventricle (B). In the right heart by-pass, measurement of left ventricular dimensions can be obtained without any interference from the right ventricle. In the total bypass preparation, cannulation of coronary arteries is shown, in this case for experiments with cardioplegic solutions.

dependence of the right and the left ventricles has been extensively demonstrated and this may complicate the analysis of experimental studies unless the right heart is bypassed [75]. The right heart bypass preparation allows global and regional left venticular function to be studied in the presence of a normal systemic circulation. Both global and regional ischaemia can be studied, in addition to the effects of hypoxia.

Bypass preparations are ideally suited to the study of cardiac protection during cardiopulmonary bypass. Using a model that can be converted from right ventricular to total bypass, Guyton and colleagues [35] have shown that perfusion with an oxygenated cardioplegic solution allows a much better recovery of function of ischaemic myocardium than perfusion with a conventional solution. Similarly, the quality of delivery of cardioplegia influences recovery of left ventricular compliance [20]. Recently, the interaction of hydrogen ions and oxygen free radicals has been implicated in the development of ischaemic/reperfusion injury [38]. Hypoxic conditions favour the univalent reduction of oxygen, which results in increased production of oxygen free radicals. These radicals are highly reactive and cytotoxic. In a cardiopulmonary bypass preparation, Stewart and his colleagues [69] have been able to show that cardioplegia with a solution containing superoxide dismutase, mannitol and potassium protected both mechanical and subcellular function when compared with cardioplegia using a standard solution.

When partial or total bypass preparations are used, regional and global left ventricular ischaemia can be obtained by constricting or occluding one or several coronary arteries. In contrast to the technique used with isolated preparations, the heart is perfused with blood; thus coronary blood flow and myocardial oxygen consumption are in the normal range. Ischaemia reduces delivery of oxygen and substrates, in addition to reducing the removal of carbon dioxide and metabolic byproducts.

Intact Heart

The intact heart is the most complex model. With it, it is possible to examine the effect of global and regional ischaemia. Ischaemia can be imposed acutely (a coronary artery is tied off), gradually (a snare is slowly tightened around the artery), or very slowly by placing an ameroid constrictor around the artery [49]. The slow swelling of this plastic material leads to complete occlusion after 2–3 weeks. Rather than occlusion, acute or chronic constriction can be established, mimicking the situation of atheromatous coronary stenosis. In the intact heart, global and regional ischaemia can be analysed in terms of ECG changes (mapping of ST segments), regional function (sonomicrometry, Walton–Brodie strain gauge arches, regional intramural pressure) and regional metabolism (sampling blood from the coronary sinus, the great cardiac vein, or from a smaller vein draining an ischaemic area). Lactate uptake and other metabolites such as glucose and fatty acids can be measured both in arterial and in coronary venous blood. Tissue Po_2 and Pco_2 can be measured by mass spectrometry or by using microelectrodes implanted into the myocardium. Regional coronary flow may be determined by repeated injections of up to six radionuclide-labelled microspheres [39] or measured by electromagnetic [42] or ultrasonic [29] flowmeters, or by clearance techniques [3]. Finally, tissues can be stained to establish the extent of myocardial infarction.

Studies of regional left ventricular wall motion have shown that mild regional ischaemia, detected by both wall motion abnormalities and lactate production, does not cause consistent changes in global left ventricular function. Epicardial ST segment abnormalities over the ischaemic zone usually appear with severe and not mild regional ischaemia [74], and are less sensitive than depression of regional wall motion [68].

Acute coronary occlusion causes significant increases in end-diastolic length associated with paradoxical systolic bulging of ischaemic segments [27, 71]. In the acutely ischaemic myocardium the time constant of relaxation may be prolonged [21] and the end-diastolic stiffness is markedly increased [1].

Mild coronary stenosis

Coronary arteries may be narrowed by the application of a balloon cuff occluder with which coronary blood flow can be reduced to a predetermined extent. A reduction by up to 20 % is considered mild. This can be achieved in chronically implanted, awake animals, or in anaesthetized animals either acutely or chronically instrumented. Depending upon the presence or absence of anaesthesia, such a reduction of flow may or may not impair regional function under resting conditions. However, mild stenosis is very likely to cause significant impairment of function when oxygen demand increases, or perfusion pressure is reduced. This is a reflection of the reduced coronary flow reserve caused by mild coronary stenosis. Over a wide range of heart rates, the transmural distribution of coronary flow is relatively uniform when the coronary arteries are normal. This indicates that active coronary vasodilatation during tachycardia compensates for the increased subendocardial compression of the coronary vessels [5]. However, when mild coronary artery stenosis has been established, a marked transmural shift in distribution occurs from the subendocardium to the subepicardium. The endocardial to epicardial flow ratio decreases from 1.15 to 0.67 with tachycardia. This demonstrates that even a mild stenosis substantially reduces the vasodilatory reserve [56]. This change in distribution of blood flow is particularly significant, since the coronary flow per beat is substantially reduced [17, 56]. Subendocardial perfusion may be reduced to 25 % of control when heart rate doubles in the presence of mild coronary artery stenosis.

In a model involving moderate coronary artery stenosis, ischaemia can be induced by acutely increasing myocardial oxygen requirements (isoproterenol, acute aortic constriction). Comparison of dysfunction assessed by sonomicrometry and by two-dimensional echocardiography has shown the latter to be both sensitive and specific for detecting transient myocardial ischaemic dyskinesia [57].

Critical coronary stenosis

Critical coronary artery stenosis is defined as a stenosis that is just tight enough to abolish the hyperaemic response following a short period (usually 10 s) of complete coronary occlusion [24, 32]. This level of coronary artery stenosis is associated with a reduction of resting coronary blood flow by up to about 25 %, depending upon the dynamic state of the circulation when the stenosis is applied. This, in turn, depends upon the type of anaesthesia [15, 16, 28, 58, 60]. As the coronary flow reserve has been abolished, the coronary vascular bed distal to the stenosis is maximally vasodilated and has lost its autoregulation. Coronary blood flow is determined by the coronary perfusion pressure and by the duration of diastole.

A further degree of complexity in the analysis of data obtained in the presence of critical coronary artery stenosis is the preservation of some epicardial vasodilator reserve. Thus, Gallagher and colleagues [30] have shown, in chronically instrumented dogs, that exercise *reduced* subendocardial blood flow but *increased* subepicardial blood flow in territories supplied by a critically stenosed coronary artery. This steal phenomenon may contribute to the reduction in subendocardial flow.

With models of critical stenosis it can be shown that coronary flow decreases sharply with diastolic arterial hypotension. This is accompanied by selective reductions in function in the area supplied by the critically narrowed vessel [15, 28] irrespective of the cause of hypotension (reduced circulating volume, depression by anaesthetic agents). Similarly, in the presence of critical coronary stenosis, the reduction of the duration of diastole that attends tachycardia reduces coronary blood flow per beat quite dramatically [17]. A limitation of the model of critical stenosis is that hypertension does not cause selective worsening of the balance between demand and supply, as is observed in coronary artery disease. With hypertension both the coronary driving pressure and coronary blood flow increase [16]. Hypertension also increases collateral blood flow.

The effects of pharmacological interventions have been extensively studied using this model. Halothane, enflurane and isoflurane cause selectively exaggerated worsening of function in territories supplied by critically narrowed coronary arteries [18, 50, 60]. Even nitrous oxide, an agent often considered to exert very little effect on the circulation, may cause selective dysfunction of myocardium supplied by a critically narrowed coronary artery [58, 62]. While the beta-blocker oxprenolol improves function of compromised myocardium [46], the calcium antagonist diltiazem causes selective depression of ischaemic myocardium [47].

By applying critical constriction to more than one coronary artery, several discrete areas of compromised blood flow may be created, involving both the right and the left ventricle (fig. 5). This makes it possible to compare the effects of the same intervention on right and left ventricular ischaemia. Using a model involving critical constriction of the left anterior descending and right coronary arteries, we have shown that isoflurane causes exaggerated depression of compromised myocardium associated with ischaemic dysfunction in both right and left ventricular myocardium [60].

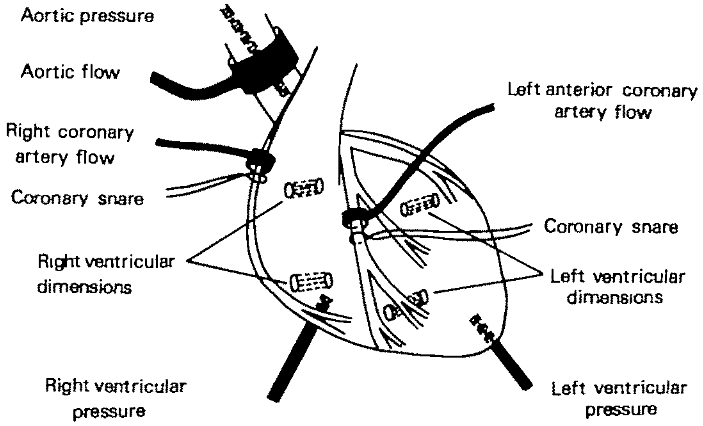

Aortic pressure
Aortic flow
Right coronary artery flow
Coronary snare
Right ventricular dimensions
Right ventricular pressure
Left anterior coronary artery flow
Coronary snare
Left ventricular dimensions
Left ventricular pressure

FIG. 5. Intact instrumented heart used to examine the effects of drugs on normal and compromised myocardium.

Coronary occlusion

By occluding a large branch of one of the main coronary arteries and by examining function in the ischaemic territory, in the border zone and in distant normal myocardium, it is possible to document the effects of interventions in three different regions. Pharmacological interventions have been extensively studied with this type of model. Theroux and his colleagues were able to show that nitroglycerin improves function in ischaemic, border zone and normal myocardium, while propranolol improves the border zone and, not surprisingly, isoprenaline causes worsening of function in ischaemic and border zones because of the tachycardia that attends its administration [71]. While most of the adverse effects of isoprenaline, and the beneficial effect of beta-adrenoceptor blockade, have been attributed to changes in global haemodynamics, including tachycardia or its blockade, recent studies have suggested that beta-blockade has beneficial effects on the energy metabolism of ischaemic myocardium; this includes a reduction in the vicious circle of fatty acid metabolism [52]. With a similar model Smith and his colleagues have shown that the calcium antagonists cause worsening of function of ischaemic and border zone segments [67].

Models of acute coronary occlusion mimic the human situation of acute coronary thrombosis, and the benefits or danger of pharmacological interventions have to be considered in the exact context of acute occlusion in the absence of a "preformed" collateral coronary circulation. The main objective of many studies using this type of model has been to determine which interventions are most likely to reduce the size of myocardial infarction. Information has been obtained by morphological studies of the heart after the animal has been sacrificed. Drugs that have been shown experimentally to reduce infarct size range from glucose–insulin–potassium solutions to halogenated anaesthetics (table III). How much is applicable to the clinical situation depends on the interval between coronary thrombosis and initiation of treatment. A difficulty of the studies of myocardial protection is that efficacy of interventions is a function, not only of the timing of that intervention, but also of the delay between intervention and morphological studies. Interventions that appear beneficial when animals are sacrificed early may have no long term effects [4].

TABLE III. *Drugs which reduce experimental infarction*

Beta-adrenoceptor blockers
Calcium influx blockers
Glyceryltrinitrate
Hydrocortisone
Hyaluronidase
Glucose–insulin–potassium
Morphine
Inhalation anaesthetic agents

In models of acute coronary occlusion it has been shown that ischaemic damage is less pronounced when coronary occlusion is effected during the administration of halogenated anaesthetics [9, 19, 73]. Halothane has also been shown to improve the ratio of oxygen availability to oxygen consumption in acutely ischaemic territories. This was associated with a higher oxygen tension in effluent venous blood of ischaemic, as opposed to normal, myocardium [66]. With the ever increasing number of coronary transluminal angioplasties that are performed, a very small minority suffer acute complications. In such patients, halogenated anaesthetics may have a beneficial effect during the period between "incident" and surgical revascularization.

Coronary artery reperfusion

The value of early reperfusion after acute coronary occlusion is of considerable importance as far as thrombolysis, coronary angioplasty and myocardial revascularization are concerned. Experimentally, reperfusion 1 or 3 h after acute coronary occlusion has been shown to enhance survival in dogs [6].

Stunned myocardium

Braunwald and Kloner [10] have developed the concept of the "stunned myocardium" based on experimental and clinical evidence of prolonged effects of brief episodes of ischaemia on myocardial ultrastructure, high energy phosphates and regional function. Such brief episodes of ischaemia (less than 20 min in duration) do not cause myocardial necrosis. Cytotoxic, oxygen-derived free radicals are known to be generated at an accelerated rate during myocardial reperfusion, and could be responsible for tissue injury. In a model involving temporary LAD occlusion, administration of sodium dismutase and catalase greatly enhanced function after reperfusion, even though high energy phosphate content was not improved [6]. Similarly, agents that either inhibit free radical formation or scavenge free radicals decrease the incidence of reperfusion-induced arrhythmias [8]. Superoxide dismutase and catalase, besides their effects after reperfusion has taken place, may also protect the function of ischaemic segments during the period of coronary occlusion. Subendocardial shortening during ischaemia is significantly greater in the presence of superoxide dismutase and catalase than in their absence [33]. These studies suggest that oxygen free radicals may play an important role in ischaemic and reperfusion injury, and their scavenging may open new avenues in the management of acute ischaemia.

Progressive coronary occlusion

Ameroid is a plastic polymer that is capable of swelling slowly when implanted around coronary arteries. This leads, after a few weeks, to the complete occlusion of the vessel [49]. During that period of time, collateral blood flow develops gradually, to the extent that function may remain normal even though "direct" flow to an area of the left ventricle has stopped, and all the blood supply comes from the newly developed collaterals. Studies with this type of model suggest that collateral blood flow is significant, not only in terms of survival of the compromised myocardium, but also in terms of its contribution to the function of the cardiac pump. Collateral blood flow is well maintained during the administration of halothane [65], while it is reduced by isoflurane [13], suggesting the development of coronary steal.

Isolated coronary perfusion

A major problem of all the models using acute partial or total coronary occlusion is that the effects of interventions may be ascribed to both direct effects on the coronary circulation, and global effect on the heart and circulation. Thus many authors have elected to study the effects of ischaemia in models using controlled perfusion of the coronary circulation, with either arterial blood (carotid–coronary bypass), or venous blood passed through an oxygenator. With such models, coronary perfusion pressure, or coronary blood flow, or both, can be set at predetermined values; keeping the coronary perfusion constant, the effects of pharmacological interventions on regional function may be examined. The effects on the heart and the circulation (enhancement or depression) will be present, but will not influence the coronary circulation because the latter is independently controlled. Forrester and colleagues have shown that reductions in coronary blood flow are accompanied by reductions in systolic function of the segment rendered gradually ischaemic, ischaemic dysfunction being characterized not only by decreased shortening, but also by abnormal patterns of contraction. These were particularly obvious when the instantaneous dynamic relationship between pressure and dimensions were examined [25, 26]. While we have shown in the intact heart that halothane selectively worsens the function of compromised myocardium [28, 50], studies by Behrenbeck and colleagues [7], using a controlled coronary circulation, have shown that halothane does not cause dysfunction of compromised myocardium when the coronary flow is maintained constant. This suggests that the selective worsening of function of the compromised myocardium in the intact heart is the result of the reductions in both coronary perfusion pressure and coronary blood flow that attend the administration of halothane, and not of a specific effect of halothane on the ischaemic myocardium.

Some models associate isolated, controlled coronary perfusion and selective stenosis of coronary arteries. With such models it is possible to investigate the effects of interventions on normal and compromised myocardium when either coronary perfusion pressure or coronary blood flow are kept constant. When flow is maintained constant, arteriolar vasodilatation reduces the coronary perfusion pressure and causes a steal from the areas supplied by collateral vessels. Thus in a canine model involving progressive occlusion of a coronary artery (ameroid constrictor) and perfusion at constant flow, isoflurane has been shown to cause a coronary steal [13].

Isolated coronary perfusion has been used to examine the active or passive nature of increased shortening of normal myocardium when a distant area is rendered ischaemic. The improvement in shortening occurs only when coronary flow is capable of increasing, thus it must be considered an active compensatory phenomenon [40]. If flow cannot increase, the normal segment may exhibit relative hypoperfusion and dysfunction.

While most studies of myocardial protection have concentrated on drugs that reduce oxygen demand or increase oxygen supply, the role of vasopressors has been less well documented. Nathan and Feigl [53], using a model of controlled coronary blood flow, have shown that noradrenaline improves the transmural distribution of coronary blood flow in territories where total flow was reduced sufficiently to cause ischaemia. This type of study forms the basis for the association of vasopressors and nitrates in myocardial ischaemia.

Coronary steal is defined as an increase in flow of non-ischaemic myocardium at the expense of decreasing collateral flow to ischaemic myocardium. In a model of left anterior descending coronary occlusion, maximum vasodilatation has been shown to cause coronary steal. Mild coronary vasodilatation produced a significant decrease in collateral flow when a proximal left circumflex coronary artery stenosis was present in addition to the occlusion of the LAD [34]. Another type of coronary steal involves redistribution of blood flow away from the subendocardium. With mild coronary artery stenosis, vasodilatation occurs in the epicardial region, while subendocardial blood flow increases only minimally. During severe stenosis, however, vasodilatation increases epicardial and decreases endocardial blood flow [34].

CONCLUSION

Models of myocardial ischaemia range from the simplest isolated heart muscle preparations to the most complex types of instrumentation of the intact heart. All models have their advantages and drawbacks. Extrapolation from these models to the human situation of myocardial ischaemia associated with coronary heart disease must be made cautiously. However, experimental models have been invaluable in the investigation of the effects of ischaemia and hypoxia on the heart; they will continue to be central to our understanding of cardiac protection and the prevention and treatment of myocardial ischaemia.

REFERENCES

1. Amano J, Thomas JX, Lavallee M, Mirsky I, Glover D, Manders WT, Randall WC, Vatner SF. Effects of myocardial ischemia on regional function and stiffness in conscious dogs. *American Journal of Physiology* 1987; **252**: H110–H117.
2. Apstein CS, Bing OHL, Levine HJ. Cardiac muscle function during and after hypoxia: effects of glucose concentration, mannitol and isoproterenol. *Journal of Molecular and Cellular Cardiology* 1975; **8**: 627–640.
3. Aukland K, Bower BF, Berliner RW. Measurement of local blood flow with hydrogen gas. *Circulation Research* 1964; **14**: 164–187.
4. Bache RJ. Can drugs really limit infarct size? In: Hearse DJ, Yellon DM, eds. *Therapeutic Approach to Myocardial Infarct Size Limitation*. Raven Press, New York, 1984; 185–208.
5. Bache RJ, Cobb FR. Effect of maximal coronary vasodilatation on transmural myocardial perfusion during tachycardia in the awake dog. *Circulation Research* 1977; **41**: 648–653.
6. Baughman KL, Maroko P, Vatner SF. Effects of coronary artery reperfusion on myocardial infarct size and survival in conscious dogs. *Circulation* 1981; **63**: 317–323.
7. Behrenbeck T, Nugent M, Quasha A, Hoffman E, Ritman E, Tinker J. Halothane and ischemic regional wall dynamics. *Anesthesiology* 1980; **53**: S140.
8. Bernier M, Hearse DJ, Manning AS. Reperfusion-induced arrhythmias and oxygen-derived free-radicals. *Circulation Research* 1986; **58**: 331–340.
9. Bland, JHK, Lowenstein E. Halothane-induced decrease in experimental myocardial ischemia in the non-failing canine heart. *Anesthesiology* 1976; **45**: 287–293.
10. Braunwald E, Kloner RA. The stunned myocardium: prolonged, postischemic ventricular dysfunction. *Circulation* 1982; **66**: 1146–1149.

11. Brutsaert DL, Paulus WJ. Loading and performance of the heart as muscle and pump. *Cardiovascular Research* 1977; **11**: 1–16.
12. Brutsaert DL, Rademakers FE, Sys SU, Gillebert TC, Housmans PR. Analysis of relaxation in the evaluation of ventricular function of the heart. *Progress in Cardiovascular Disease* 1985; **28**: 143–163.
13. Buffington CW, Romson JL, Levine A, Duttlinger NC, Huang AH. Isoflurane induces coronary steal in a canine model of chronic coronary occlusion. *Anesthesiology* 1987; **66**: 280–292.
14. Carter JE, Falacios I, Frist WH, Rosenthal S, Newell JB, Powell WJ jr. Improvement in relaxation by nifedipine in hypoxic isometric cat papillary muscle. *American Journal of Physiology* 1986; **250**: H208–H212.
15. Coetzee A, Foëx P, Holland DE, Ryder WA, Jones LA. Effect of hypoxia on the normal and ischemic myocardium. *Critical Care Medicine* 1984; **12**: 1027–1031.
16. Coetzee A, Foëx P, Holland D, Ryder A, Jones LA. Coronary blood flow during variation in coronary perfusion pressure. *South African Medical Journal* 1985; **68**: 15–19.
17. Coetzee A, Holland D, Foëx P, Ryder A, Jones LA. Myocardial ischaemia during tachycardia—not due to an increase in myocardial oxygen demand. *South African Medical Journal* 1985; **67**: 496–499.
18. Cutfield, GR, Francis CM, Foëx P, Lowenstein E, Davies WL, Ryder WA. Myocardial function and critical constriction of the left anterior descending coronary artery: effect of enflurane. *British Journal of Anaesthesia* 1980; **52**: 953P–954P.
19. Davis RF, Frank LP. Isoflurane decreases myocardial infarct size after left anterior descending coronary occlusion in dogs. *Anesthesiology* 1985; **63**: A12.
20. Dorsey LM, Colgan TK, Silverstein JI, Hatcher CR jr, Guyton RA. Alterations in regional myocardial function after heterogenous cardioplegia. *Journal of Thoracic and Cardiovascular Surgery* 1983; **86**: 70–79.
21. Doyle RL, Foëx P, Ryder WA, Jones LA. Differences in ischaemic dysfunction following gradual vs abrupt coronary occlusion: Effects on isovolumic relaxation. *Cardiovascular Research* 1987; **21**: 507–514.
22. Edlund A, Wennmalm A. Oxygen consumption in rabbit Langendorff hearts perfused with a saline medium. *Acta Physiologica Scandinavica* 1981; **113**: 117–122.
23. Edman KAP, Nilsson E. The mechanical parameters of myocardial contraction studied at constant length of the contractile element. *Acta Physiologica Scandinavica* 1968; **72**: 205–219.
24. Elzinga WE, Skinner DB. Hemodynamic characteristics of critical stenosis in canine coronary arteries. *Journal of Thoracic and Cardiovascular Surgery* 1975; **69**: 217–222.
25. Foëx P, Francis CM, Cutfield GR, Leone B. The pressure–length loop. *British Journal of Anaesthesia* 1988; **60**: 65S–71S.
26. Forrester JS, Tyberg JV, Wyatt HL, Goldner S, Parmley WW, Swan HJC. Pressure–length loop: a new method for simultaneous measurement of segmental and total cardiac function. *Journal of Applied Physiology* 1974; **37**: 771–775.
27. Forrester JS, Wyatt HL, Da Luz PL, Tyberg JV, Diamond GA, Swan HJC. Functional significance of regional ischemic contraction abnormalities. *Circulation* 1976; **54**: 64–70.
28. Francis CM, Foëx P, Lowenstein E, Glazebrook C, Davies WL, Ryder WA, Jones LA. The interaction between regional myocardial ischaemia and left ventricular performance under halothane anaesthesia in the dog. *British Journal of Anaesthesia* 1982; **54**: 965–980.
29. Franklin DL, Schlegel E, Ruschmer RF. Blood flow measured by Doppler frequency shift of back-scattered ultrasound. *Science* 1961; **134**: 564–567.
30. Gallagher KP, Osakada G, Matsuzaki M, Kemper WS, Ross J jr. Myocardial blood flow and function with critical coronary stenosis in exercising dogs. *American Journal of Physiology* 1982; **12**: H698–H707.
31. Goldberg AM, Sohn UZ, Phear WPC. Direct myocardial effects of N_2O. *Anesthesiology* 1972; **37**: 373–380.
32. Gould KL, Lipscomb K, Hamilton GW. Physiologic basis for assessing critical coronary stenosis. *American Journal of Cardiology* 1974; **33**: 87–94.
33. Gross GJ, Farber NE, Hardmann HF, Warlier DC. Beneficial action of superoxide dismutase and catalase in stunned myocardium. *American Journal of Physiology* 1986; **250**: H372–H377.
34. Gross GJ, Warltier DC. Coronary steal in four models of single or multiple vessel obstruction in dogs. *American Journal of Cardiology* 1981; **48**: 84–92.
35. Guyton RA, Dorsey LM, Craver JM, Bone DK, Jones EL, Murphy DA, Hatcher CR jr. Improved myocardial recovery after cardioplegic arrest with an oxygenated crystalloid solution. *Journal of Thoracic and Cardiovascular Surgery* 1985; **89**: 877–887.
36. Hearse DJ, Humphrey SM, Bullock GR. Reoxygenation, reperfusion and the calcium paradox: studies of cellular damage and enzyme release. In: Hearse DJ, de Leiris J, eds. *Enzymes in Cardiology: Diagnosis and Research.* Chichester: John Lesley, 1979; 417–444.
37. Henderson AH, Brutsaert DL. An analysis of the mechanical capabilities of heart muscle during hypoxia. *Cardiovascular Research* 1973; **7**: 763–776.
38. Hess ML, Manson NH, Okabe E. The role of free radicals in the pathophysiology of ischemic heart disease. *Canadian Journal of Physiology and Pharmacology* 1983; **60**: 1382–1385.
39. Heymann MA, Payne BD, Hoffman JIE, Rudolph AN. Blood flow measurement with radionuclide-labelled microspheres. *Progress in Cardiovascular Diseases* 1977; **10**: 55–79.
40. Homans DC, Sublett E, Elsperger KJ, Schwartz JS, Bache RJ. Mechanisms of remote myocardial dysfunction during coronary artery occlusion in the presence of multivessel disease. *Circulation* 1986; **74**: 588–596.
41. Janicki JS, Reeves RC, Weber KT, Donald TC, Walker AA. Application of a pressure servo system developed to study ventricular dynamics. *Journal of Applied Physiology* 1974; **37**: 736–741.
42. Khouri EM, Gregg DE. Miniature electromagnetic flow meter applicable to coronary arteries. *Journal of Applied Physiology* 1963; **18**: 224–227.
43. Kim M-S, Akera T. O_2 free radicals: cause of ischemia-reperfusion injury to cardiac Na^+–K^+-ATPase. *American Journal of Physiology* 1987; **252**: H252–H257.
44. Langendorff O. Untersuchungen am liberlebenden Saugertierherzen. *Pflugers Archives fur die Gesamte Physiologie des Menschen und der Tiere* 1895; **61**: 291–332.
45. de Leiris J, Harding DP, Pestre S. The isolated perfused rat heart: a model for studying myocardial hypoxia or ischaemia. *Basic Research in Cardiology* 1984; **79**: 313–321.
46. Leone BJ, Lehot J-J, Francis CM, Cutfield GR, Foëx P.

Beta-blockade reverses regional dysfunction in ischemic myocardium. *Anesthesia and Analgesia* 1987; **66**: 607–614.

47. Leone BJ, Philbin DM, Lehot JJ, Wilkins M, Foëx P, Ryder WA. Intravenous diltiazem worsens regional function in compromised myocardium. *Anesthesia and Analgesia* 1988; **67**: 205–210.
48. Little RC. The effect of acute hypoxia on the viscoelastic properties of the myocardium. *American Heart Journal* 1976; **92**: 609–614.
49. Litvak J, Siderides LE, Vineberg AM. The experimental production of coronary artery insufficiency and occlusion. *American Heart Journal* 1957; **53**: 505–518.
50. Lowenstein E, Foëx P, Francis CM, Davies WL, Yusuf S, Ryder WA. Regional ischemic ventricular dysfunction in myocardium supplied by a narrowed coronary artery with increasing halothane concentrations. *Anesthesiology* 1981; **55**: 349–359.
51. Malloy CR, Matthews PM, Smith MB, Rodda GK. Influence of propranolol on acidosis and high energy phosphates in ischaemic myocardium of the rabbit. *Cardiovascular Research* 1986; **20**: 710–720.
52. Nanki M, Itoh K-I, Matsubara T, Nishimura K, Kambe T, Sugiyama S, Ozawa T, Sakamoto N. Evaluation of the effect of metoprolol on energy metabolism in the ischaemic myocardium in relation to regional myocardial blood flow. *Cardiovascular Research* 1987; **21**: 660–667.
53. Nathan HJ, Feigl EO. Adrenergic vasoconstriction lessens transmural steal during coronary hypoperfusion. *American Journal of Physiology* 1986; **250**: H645–H653.
54. Nayler WG, Ferrari R, Williams A. Protective effect of pretreatment with verapamil, nifedipine and propranolol on mitochondrial function in the ischemic and reperfused myocardium. *American Journal of Cardiology* 1980; **46**: 242–248.
55. Neely, JR, Liebermeister H, Battersby EJ, Morgan HE. Effect of pressure development on oxygen consumption by isolated rat hearts. *American Journal of Physiology* 1967; **212**: 804–814.
56. Neill WA, Oxendine J, Phelps N, Anderson RP. Subendocardial ischemia provoked by tachycardia in conscious dogs with coronary stenosis. *American Journal of Cardiology* 1975; **35**: 30–36.
57. Pandian NG, Kerber RE. Two-dimensional echocardiography in experimental coronary stenosis. I. Sensitivity and specificity in detecting transient myocardial dyskinesis: comparison with sonomicrometers. *Circulation* 1982; **66**: 597–602.
58. Philbin DM, Foëx P, Drummond G, Lowenstein E, Ryder WA, Jones LA. Postsystolic shortening of canine left ventricle supplied by a stenotic coronary artery when nitrous oxide is added in the presence of narcotics. *Anesthesiology* 1985; **62**: 166–174.
59. Price HL, Helrich M. Myocardial depression by nitrous oxide and its reversal by Ca^{2+}. *Anesthesiology* 1976; **44**: 211–214.
60. Priebe H-J, Foëx P. Isoflurane causes regional myocardial dysfunction in dogs with critical coronary artery stenoses. *Anesthesiology* 1987; **66**: 293–300.
61. Przyklenk K, Kloner RA. Superoxide dismutase plus catalase improve contractile function in the canine model of the "stunned myocardium". *Circulation Research* 1986; **58**: 148–156.
62. Ramsay JG, Arvieux CC, Foëx P, Philbin DM, Jeavons P, Ryder WA, Jones LA. Regional and global myocardial function in the dog when nitrous oxide is added to halothane in the presence of critical coronary artery constriction. *Anesthesia and Analgesia* 1986; **65**: 431–436.
63. Rovetto MJ, Whitmer JT, Neely JR. Comparison of the effects of anoxia and whole heart ischemia on carbohydrate utilization in isolated working hearts. *Circulation Research* 1973; **32**: 699–701.
64. Salama G, Lombardi R, Elson J. Maps of optical action potentials and NADH fluorescence in intact working hearts. *American Journal of Physiology* 1987; **252**: H384–H394.
65. Sivarajan M, Bashein G. Effect of halothane on coronary collateral circulation. *Anesthesiology* 1985; **62**: 588–596.
66. Smith G, Rogers K, Thorburn J. Halothane improves the balance of oxygen supply to demand in acute experimental myocardial ischaemia. *British Journal of Anaesthesia* 1980; **52**: 577–583.
67. Smith HJ, Goldstein RA, Griffith JM, Kent KM, Epstein SE. Regional contractility: selective depression of ischemic myocardium by verapamil. *Circulation* 1976; **54**: 629–635.
68. Smith HJ, Kent KM, Epstein SE. Relationship between regional contractile functional and ST segment elevation after experimental coronary artery occlusion in the dog. *Cardiovascular Research* 1978; **12**: 444–448.
69. Stewart JR, Blackwell WH, Crute SL, Loughlin V, Greenfield LJ, Hess WL. Inhibition of surgically induced ischemia/reperfusion injury by oxygen free radical scavengers. *Journal of Thoracic and Cardiovascular Surgery* 1983; **86**: 262–272.
70. Taegtmeyer H, Hems R, Krebs HA. Utilization of energy-providing substrates in the isolated working heart. *Biochemical Journal* 1980; **186**: 701–711.
71. Theroux P, Franklin D, Ross J jr, Kemper WS. Regional myocardial function during acute coronary artery occlusion, and its modification by pharmacologic agents in the dig. *Circulation Research* 1974; **35**: 896–908.
72. Tyberg JV, Yeatman LA, Parmley WW, Urschel CW, Sonnenblick EH. Effects of hypoxia on mechanics of cardiac contraction. *American Journal of Physiology* 1970; **218**: 1780–1788.
73. Van Ackern K, Mittmann U, Bruckner UB, Vetter HO, Madler C, Victor H. Concept in patients with hypertension and coronary heart disease—Clinical and experimental aspects. In: Peter K, Jesch F, eds. ***Inhalation Anaesthesia Today and Tomorrow***. Berlin: Springer-Verlag, 1982; 205–218.
74. Waters DD, DaLuz P, Wyatt HL, Swan HJC, Forrester JS. Early changes in regional and global left ventricular function induced by graded reduction in regional coronary perfusion. *American Journal of Cardiology* 1977; **39**: 537–543.
75. Weber KT, Janicki JS, Shroff SG, Linkoff MJ. The cardiopulmonary unit. *Clinics in Chest Medicine* 1983; **2**: 101–110.
76. Wetstein L, Simson MB, Feldman PD, Harken AH. Pharmacologic modifications of myocardial ischemia. *Circulation* 1982; **66**: 548–554.

Br. J. Anaesth. (1988), **61**, 56–67

ANAESTHESIA AND ISCHAEMIC HEART DISEASE: LABORATORY RESULTS

D. KETTLER AND A. HOEFT

The major problem in ischaemic heart disease, not only during anaesthesia, is a threatened imbalance between oxygen demand by and oxygen supply to the myocardium. In many patients who suffer from coronary artery disease, acute ischaemia is not present when they enter the operating theatre, but induction and maintenance of anaesthesia, in addition to surgical stress, may alter in a detrimental manner the balanced relationship between oxygen demand and supply.

A considerable amount of experimental work has been devoted to the question of how myocardial oxygen consumption and coronary blood flow are influenced by various types of anaesthesia and whether or not ischaemia may result from haemodynamic disturbances associated with anaesthesia and surgery. It is not possible to discuss all the laboratory studies that have been published within the past years. The investigations which are considered in this paper are therefore not complete, but reflect personal choice.

Effects of anaesthesia on myocardial oxygen demand and oxygen supply

Since ischaemic heart disease is mainly a problem of the balance between cardiac energy requirements and coronary blood supply, it is logical first to consider the physiological factors determining oxygen demand and oxygen supply in the heart, and to examine how these determinants are altered by anaesthesia.

Figure 1 summarizes the essential determinants of myocardial energy demand and supply. The basal metabolism of the heart, which is of the order of 1.0 ml of oxygen/100 g of myocardial tissue, is only a minor part of the overall energy consumption. The prevailing energy demand results from cross-bridge interactions. Since the number of active cross-bridges per unit of time is not assessable, the estimation of myocardial energy demand depends more or less on indirect haemodynamic indices [3, 44]. It is commonly accepted that an increase in heart rate, left ventricular pressure or systolic wall tension is associated with an enhancement of myocardial energy demand.

The myocardial oxygen supply, which depends on coronary blood flow, is influenced partly by the same determinants (for review see [24]). The amount of blood flowing through the coronary vascular bed is the result of the driving pressure gradient and of the coronary resistance, which depends on vascular tone and on an extravascular component. The latter is influenced mainly by heart rate and diastolic wall tension. Under physiological conditions coronary vascular tone is well controlled to match blood supply and metabolic demands. The fundamental mechanisms which are responsible for this autoregulation are still not well understood. There is evidence that metabolic control plays the major role in the normal heart. However, as discussed below, sympathetic control of the coronary circulation, in particular alpha-adrenergic vasoconstriction, might be important under pathophysiological conditions.

In principle, all anaesthetics have direct and indirect cardiodepressant effects, thus reducing myocardial systolic wall tension and arterial pressure. The direct negative inotropic action of opioids and volatile anaesthetics have been demonstrated most clearly in experiments with isolated preparations [10, 26, 27, 42, 43, 54, 74, 80, 86]. However, in clinical practice only myocardial depression produced by volatile anaesthetics is important. One mechanism that could contribute to the cardiodepressant effect of the volatile anaesthetics was suggested to be interference with the slow calcium channel [50–53, 61] in addition to disturbance of calcium transport by the sarcoplasmic reticulum [6, 18, 46, 55, 81, 82].

D. KETTLER, M.D.; A. HOEFT, M.D.; Zentrum Anästhesiologie der Universität Göttingen, Robert-Koch-Str. 40, D-3400 Göttingen, West Germany.

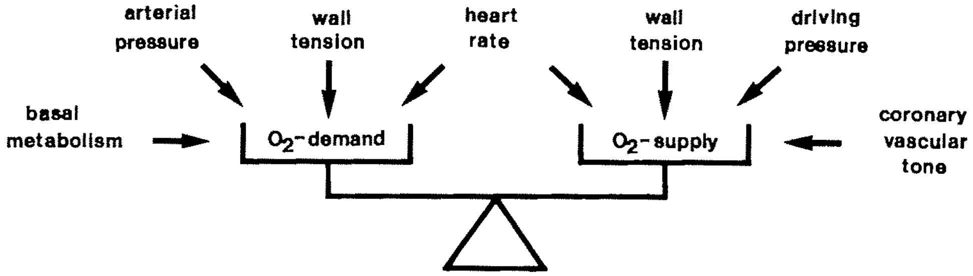


FIG. 1. Determinants of myocardial oxygen supply and oxygen demand. Myocardial oxygen supply and demand are in part influenced by the same determinants. For details refer to text.

A direct negative chronotropic effect of halothane, enflurane and isoflurane has also been observed on the isolated sino-atrial node [8]. However, *in vivo*, this direct effect is often counteracted by reflex mechanisms which compensate for the loss of inotropism. Such an effect was observed by Merin and colleagues [64–66]. In a study in chronically instrumented dogs, halothane and enflurane exerted an expected decrease in left ventricular pressure, stroke volume and cardiac output, but there was an increase in heart rate. Since an increase in heart rate increases myocardial energy demand, but a decreased inotropic state is expected to reduce cardiac energy consumption, the net effect on oxygen demand is not easy to predict. However, Merin also measured arterio-coronary venous oxygen differences and myocardial blood flow by a xenon clearance method. Halothane, in addition to enflurane, reduced myocardial blood flow and oxygen consumption. Oxygen extraction decreased and lactate extraction increased. Thus oxygen supply to the heart continued to match energy demands (fig. 2).

A similar reduction in oxygen demand has been demonstrated experimentally for isoflurane [60]. However, it is now widely accepted that isoflurane, in common with ether, has coronary vasodilating properties [5,21,25,32]. This coronary vasodilating action was confirmed recently in a study by Sill and colleagues [75] on dogs in a closed chest preparation. Myocardial blood flow was measured by microspheres. When oxygen consumption ($\dot{V}mo_2$) was compared with coronary blood flow, it became evident that, for a given rate of $\dot{V}mo_2$, coronary flow was greater following isoflurane. Thus myocardial oxygen extraction decreased and isoflurane had clearly exerted coronary vasodilating properties.

In summary, results of laboratory studies indicate that anaesthetics have the following effects on myocardial oxygen demand and oxygen supply of the normal heart:

(1) All anaesthetics have more or less direct and indirect cardiodepressant properties. The direct

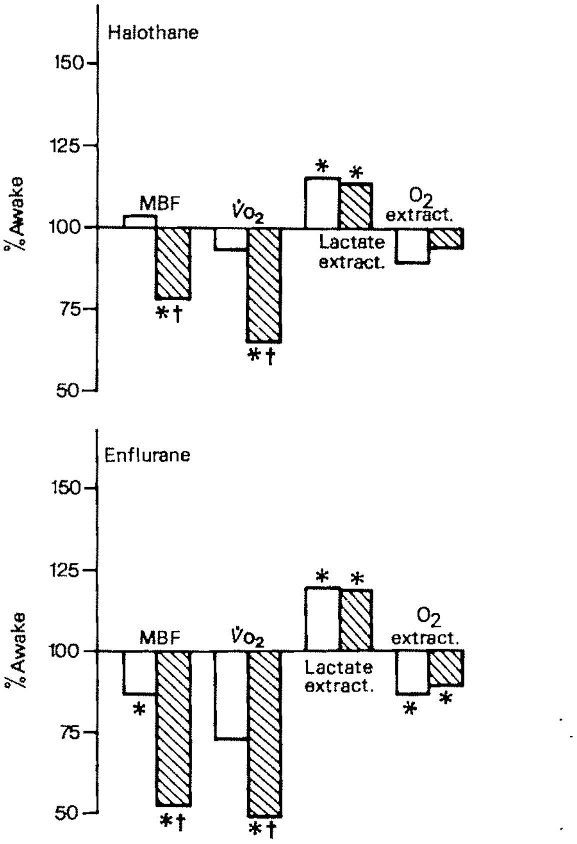


FIG. 2. Comparison of the effects of halothane and enflurane on myocardial blood flow and oxygen demand in experiments with chronically instrumented dogs, performed by Merin [65]. MBF = Myocardial blood flow; $\dot{V}O_2$ = myocardial oxygen consumption. Open columns = low doses; cross-hatched columns = high doses. $*P < 0.05$ *v.* awake; $\dagger P < 0.05$ *v.* low dose.

negative inotropic effect of opioids is probably not of clinical significance.

(2) The negative chronotropic effect of volatile anaesthetics is counteracted *in vivo* by reflex mechanisms, which may lead to tachycardia and lessen the degree of the cardiodepressant oxygen-saving effect.

(3) With the exception of isoflurane (and ether), anaesthetics have no direct effects on coronary autoregulatory control.

Is a "low demand–low pressure" or a "high demand–high pressure" anaesthetic regimen more protective against myocardial ischaemia?

Unfortunately, laboratory data on the effects of anaesthetics on myocardial energy demand and coronary blood flow are of little significance for the heart with impaired coronary vascular reserve. It cannot be predicted if, in the presence of a coronary artery stenosis, volatile agents reduce oxygen demand in parallel with a reduction in driving pressure. In addition, it is possible that the rules which govern the energy turnover of non-ischaemic areas do not necessarily hold for the energy demand of ischaemic tissue.

Extensive experimental work has therefore been carried out to approach this problem. In most investigations, animal models with coronary artery occlusion or coronary artery stenosis were used. In the classical initial study of Bland and Lowenstein [7], repeated occlusions of a coronary artery were used and the results seemed to be encouraging. It was found that the infarct size, measured by the sum of ST-segment elevations, was reduced by administration of halothane (fig. 3). In other words, a low driving pressure and low demand situation seemed to be more favourable for the heart. In the following years several other investigators came to the same conclusion, using halothane [30, 70, 77, 84]. Smith and co-workers investigated the effect of halothane in an open chest dog model after 1 h of coronary occlusion with more sophisticated methods [78]. They found that administration of halothane increased the $P\text{O}_2$ in a collateral vein adjacent to the occluded artery. Regional blood flow was measured also, using a xenon clearance technique. The calculated ratio of oxygen availability was enhanced and it was concluded that halothane improved the balance of oxygen supply to demand in acute myocardial ischaemia.

However, as observed later by Merin, Verdouw and De Jong [66], in most instances halothane was administered to animals already anaesthetized and heart rates and arterial pressures under control conditions were relatively high. The administration of the anaesthetic under investigation resulted in a decrease in these determinants of oxygen

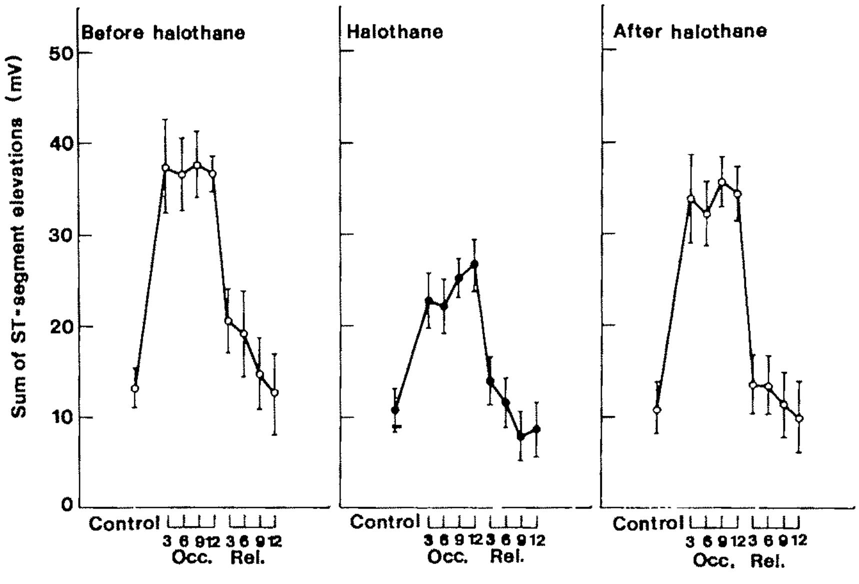


FIG. 3. Sum of ST-segment elevations before, during and after administration of 0.75 % halothane (six dogs). In this study by Bland and Lowenstein [7] the severity of ischaemia was reduced during halothane anaesthesia.

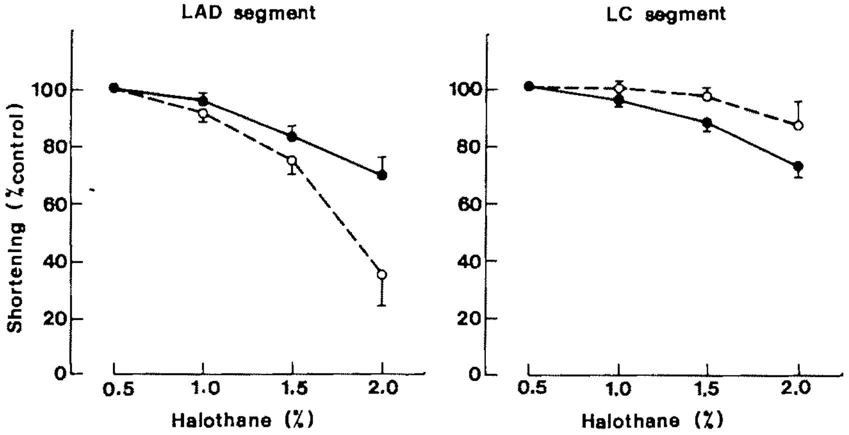


FIG. 4. Effect of increasing concentrations of halothane before (●–●) and after (○–○) constriction of the left anterior descending (LAD) artery. During constriction the LAD segment shortened less at each concentration of halothane. This became significant at 2%. In contrast, the function of the control left circumflex (LC) segment was preserved. From Lowenstein and colleagues [48].

demand, leading to a beneficial effect on the oxygen supply and demand relationship [7, 59, 66]. This was demonstrated most clearly by the study of van der Vusse and colleagues [85], who investigated the effect of fentanyl. The beneficial effect of fentanyl on ischaemic stress, as assessed by metabolic indices, was abolished when heart rate was held constant by atrial pacing.

In 1981, Lowenstein and associates [48] published an animal study, in which the effects of increasing halothane concentrations were investigated on regional wall shortening in addition to global and myocardial haemodynamics. In this study no significant changes of heart rate were observed when halothane was increased in a stepwise fashion, but a decrease in systolic and diastolic arterial pressures occurred. Under these experimental conditions they found that halothane had a detrimental rather than a beneficial effect. During constriction of the left anterior descending artery (LAD), the corresponding segments shortened less at each concentration of halothane than during control conditions. In contrast, the function of the control segment within the area supplied by the circumflex coronary artery was preserved (fig. 4).

Using metabolic measurements in young pigs with coronary artery stenosis for the comparison of fentanyl with halothane, Merin, Verdouw and De Jong [66] found that both types of anaesthesia were associated with high heart rates under control conditions (118 and 133 beat min^{-1}, respectively). When LAD flow was restricted to 60% of control values, an additional increase of heart rate was observed. Even though the two anaesthetics were associated with markedly different haemodynamic variables and myocardial oxygen requirements, coronary stenosis led to the same degree of metabolic signs of ischaemia. Comparable amounts of lactate, inosine, hydrogen ions and potassium were released into the coronary sinus during ischaemia. Merin concluded that neither fentanyl nor halothane protected against ischaemia and that the degree of ischaemia was similar. In an editorial view in the same issue of *Anesthesiology*, Lowenstein and colleagues [49] raised objections against this interpretation of Merin's data, on the grounds that coronary constrictions which produce the same reduction of blood flow in different haemodynamic situations are not really comparable. Using the data of Merin, he calculated that a stenosis with a cross-sectional area permitting 50% of coronary blood flow under halothane anaesthesia would permit less than 50% of blood flow under fentanyl anaesthesia. He deduced that a "low demand–low pressure" anaesthetic is better tolerated than a "high demand–high pressure" anaesthetic. However, it is also possible to dispute these conclusions. The assumption that, under all circumstances, 50% of blood flow in the absence of constriction is the smallest quantity compatible with satisfactory myocardial oxygenation might not be valid. It is conceivable that the fate of an endangered area is dependent not only on global myocardial energy demand, but also on a certain amount of substrate and oxygen supply necessary to maintain structure and integrity of the tissue.

In a more recent animal study in an open chest preparation with coronary artery stenosis, assessment of regional metabolic ischaemic indices, regional myocardial wall function and regional blood flow using microspheres was performed by van Ackern and colleagues [2]. LAD flow was constricted such that arterial inflow was reduced by 80%. In this study basic anaesthesia was maintained using nitrous oxide (and alcuronium) alone, which may explain heart rates of the order of 170 beat min^{-1} during control measurements. As expected, LAD constriction provoked severe impairment of regional wall function, regional blood flow and release of lactate into the selectively cannulated coronary vein. Administration of enflurane during LAD stenosis did not result in significant improvement in regional wall function or blood flow. A protective effect was found only in respect of local lactate extraction rates. In those animals which received enflurane, lactate release into the local vein was significantly less than in the control group. However, it should be noted that, in this study, heart rate was initially very high and significantly reduced by the administration of enflurane. In a subsequent investigation, the same group compared enflurane and isoflurane using the same experimental model [1]. Basic anaesthesia was maintained by continuous administration of piritramide. The results for enflurane were identical to those of the previous study, indicating an improvement in regional lactate extraction by the ischaemic myocardium. In contrast to the recently published investigation by Priebe and Foëx [68], beneficial rather than detrimental effects were observed with low concentrations of isoflurane. Local metabolism was improved, as indicated by reduction in lactate release into the local coronary vein. Higher concentrations of isoflurane had no effect on release of lactate.

The main problems with the studies of van Ackern involve the requirements for baseline anaesthesia. Administration of enflurane resulted in a decreased heart rate, whereas heart rate in the isoflurane group was already much lower during baseline anaesthesia.

Zimpfer and associates [86] have attempted to avoid these patterns by an experimental approach using chronically instrumented dogs. With enflurane, they found an increase in heart rate and a decrease in arterial pressure compared with the conscious state. When anaesthesia was induced in animals with chronic ischaemia, neither improvement nor specific impairment of regional wall function of the hypokinetic segment occurred [57]. Similar results were obtained for halothane [56] and isoflurane [87]. The accompanying decrease in regional systolic wall function was the same in the normal and in the hypokinetic ischaemic segment. While isoflurane decreased the contractile function of both segments, no exaggerated ischaemic myocardial dysfunction was noted. They concluded that myocardial ischaemia is not aggravated by volatile anaesthetic agents.

These findings with isoflurane are surprising. As mentioned above, isoflurane dilates coronary vessels. It is commonly accepted that coronary vasodilatation may lead to the so called "coronary steal phenomenon" when the site of vasodilatation is located preferentially within the small vessels. Indeed, this appears to occur with isoflurane. In the investigation of Sill [75], the cross-sectional areas of the coronary arteries were measured by angiography while different concentrations of isoflurane were applied. A comparison of the cross-sectional areas of the vessels and the perfusion pressure revealed that isoflurane has no influence on the diameter of epicardial vessels. The size of the vessels was dependent predominantly on perfusion pressure (fig. 5). The vasodilating effect of isoflurane, therefore, must act preferentially on small coronary vessels. It is well known that drugs with such properties, for example dipyridamole or adenosine, can evoke coronary steal phenomena.

The theoretical hypothesis that isoflurane can cause a steal phenomenon (in common with dipyridamole) has more recently been confirmed experimentally. Buffington [11] determined regional myocardial blood flow in dogs with chronic coronary occlusion using the microsphere technique and he obtained transmural samples of myocardium from the normal and the collateral dependent zone. Isoflurane increased blood flow to the normal zone at the expense of blood flow to the inner layers of the collateral dependent zone (fig. 6). Isoflurane also disturbed the distribution of blood flow between the endo- and epicardium. Under normal circumstances blood flow is slightly greater in the inner than in the outer layers. During isoflurane anaesthesia the endo:epi ratio might even be inverted in the collateral dependent zone.

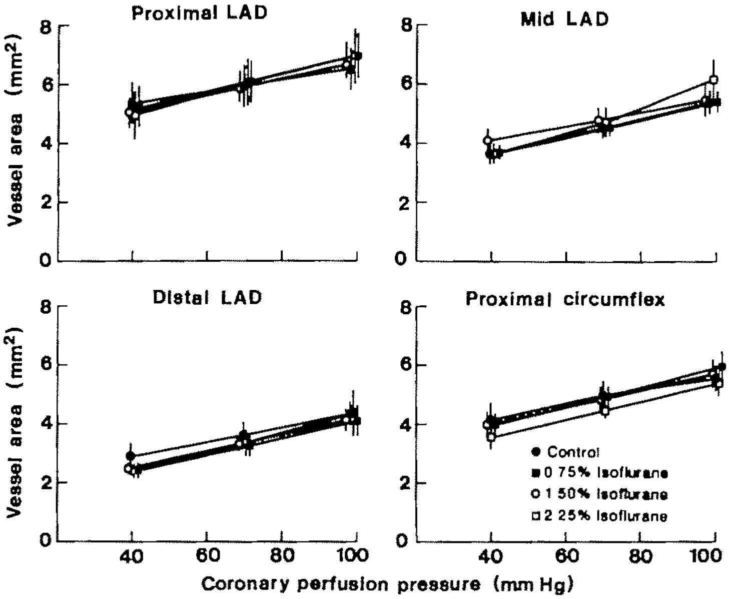


FIG. 5. Cross-sectional area of coronary arteries (measured by angiography) plotted against coronary perfusion pressure. It is evident that during isoflurane the cross-sectional areas are solely pressure dependent. Data from Sill and colleagues [75].

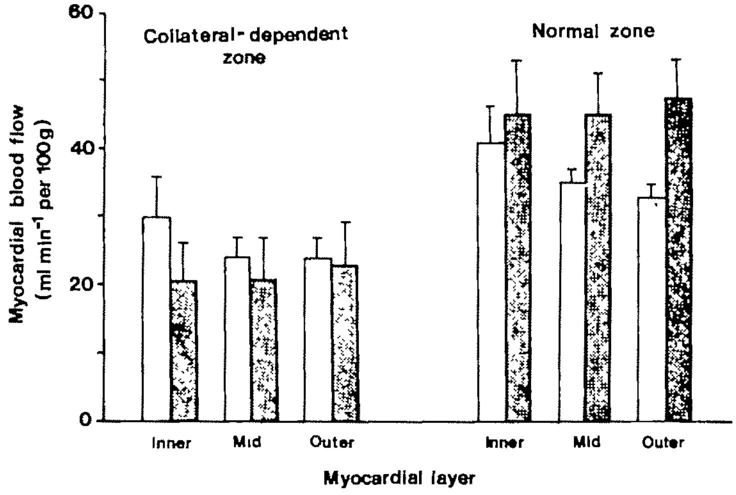


FIG. 6. Transmural distribution of myocardial blood flow (mid flow range, mean + SEM) during coronary constriction (80 % flow reduction) in the absence (□) and presence (■) of isoflurane (0.94 % end-tidal) (seven days). The addition of isoflurane increased blood flow to the outer layers of the normal zone at the expense of blood flow to the inner layers of the collateral-dependent zone. Data from Buffington and colleagues [11].

Corresponding impairment of regional wall function, that is regional akinesis, paradoxical motion and postsystolic shortening were observed by Priebe and Foëx [68] in a study with a critical coronary stenosis. Although coronary stenosis alone did not lead to impairment of myocardial function within the ischaemic area, isoflurane in low and high concentrations led to a significant reduction of myocardial segment length shortening.

Thus there are still contradictory experimental data in this field. However, the following broad general conclusions may be reached:

(1) Laboratory data on low demand–low supply or high demand–high supply anaesthesia are inconsistent. The question therefore of which type of anaesthesia is preferable for the ischaemic heart is still unresolved.

(2) There is evidence that heart rate may play a role. In most studies where heart rate was decreased by anaesthesia, a beneficial effect was observed.

(3) Isoflurane seems to induce detrimental rather than beneficial effects in higher concentrations by producing coronary steal.

Therapeutic approaches for the protection of the myocardium against ischaemia

In addition to an appropriate anaesthetic technique and haemodynamic management, additional therapeutic efforts may be made to improve the balance between myocardial oxygen demand and supply. Several pharmacological approaches with drugs such as nitrates, calcium channel blockers and beta-blockers have been investigated experimentally and are clinically well established. However, during anaesthesia most of these compounds have unfavourable side effects which lead to hypotension, bradycardia or AV block [9, 12–15, 35, 37–41, 61–63, 69, 71, 76, 82, 83] and may induce myocardial ischaemia. Pharmacological alternatives with less haemodynamic effects are therefore desirable. Two principal approaches are theoretically possible: to improve the economy of myocardial oxygen usage or to improve blood flow through the poststenotic vascular bed; or both.

From the theoretical point of view, inhibition of free fatty acid uptake in favour of carbohydrate metabolism should be advantageous during myocardial ischaemia [67]. However, glucose–insulin–potassium, as advocated by the Sodi-Pallares group [79], was not as successful as expected [58]. In particular, the hyperosmolarity of glucose-enriched solutions seems to impair the protective effects of glucose [36]. It is possible that newer compounds which induce a pharmacological shift of cardiac metabolism with reduction in FFA utilization may be of more clinical value [47].

Improvement in poststenotic blood supply by the administration of vasodilators is of limited value, since a greater degree of coronary steal might occur (see above) because of their site of action. However, there are indications that the eicosanoid metabolism plays an unfavourable role during the development of myocardial ischaemia; in particular, thromboxane A2 may be critically involved in the pathophysiology of myocardial ischaemia by constricting blood vessels, inducing platelet aggregation and by increasing the permeability of cellular membranes [16, 17, 22, 31, 72]. An attractive approach is to inhibit thromboxane synthesis selectively, thereby to redirect endoperoxide metabolism towards vasodilating prostacycline metabolites [20]. This approach is currently under investigation [33].

Until recently, it has been generally held that the amount of blood flow through a stenotic coronary artery is solely pressure dependent, once the poststenotic vessels are dilated fully by metabolic autoregulatory mechanisms [4, 23, 34, 73, 84]. However, this simplistic view is probably not valid. Interesting fundamental research work on this topic has been carried out by Heusch and co-workers [28, 29].They used an open chest dog model with critical coronary artery stenosis and measurements of poststenotic perfusion pressure, blood flow and lactate release into the coronary sinus. It was demonstrated that, distal to a severe coronary stenosis, where vasodilatory reserve should theoretically be exhausted, a poststenotic vessel constriction could still be induced by sympathetic nerve stimulation [28]. Severe stenosis associated with ischaemia is also known to be associated with increased sympathetic nerve activity [29] which, in common with experimental sympathetic stimulation, is accompanied by a significant increase in end-diastolic distal coronary resistance and a net production of lactate (fig. 7).

It is important to determine if this type of feedback mechanism can be prevented. In a subsequent study using the same model, but with blockade of the alpha-2-receptors by rauwolscine, Heusch and co-workers showed that specific interventions are possible. Compared with untreated animals, poststenotic coronary resistance remained low during sympathetic stimulation. Although lactate consumption decreased, net lactate uptake was maintained, in contrast to control animals in which lactate was produced during sympathetic stimulation. Unfortunately, rauwolscine is toxic and not available clinically, but it has been shown that nifedipine acts in a similar manner [29]. The poststenotic, alpha-2-

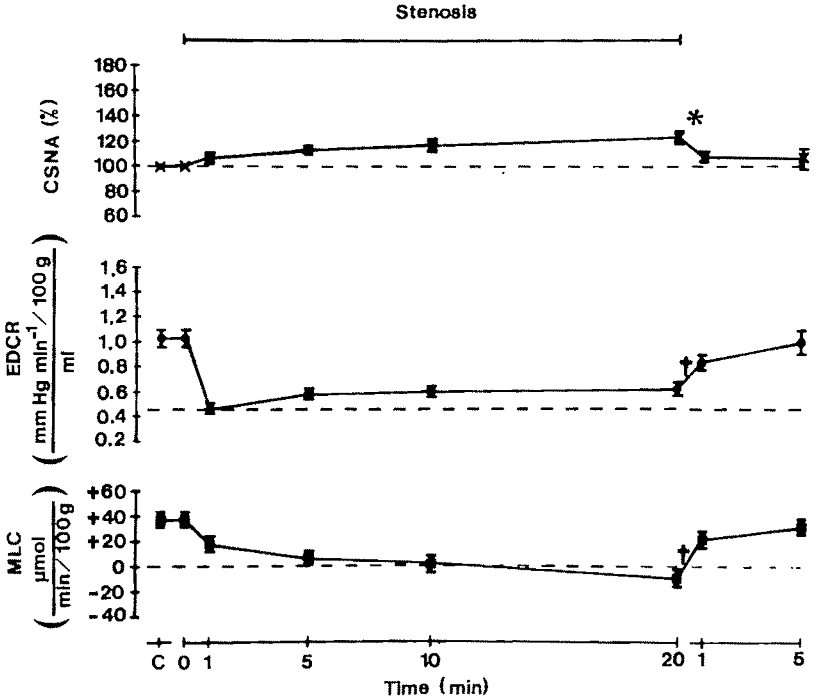


FIG. 7. The effects of 20 min of acute coronary stenosis on cardiac sympathetic nerve activity (CSNA), end-diastolic distal coronary resistance (EDCR) and myocardial lactate consumption (MLC) in 23 dogs. During coronary stenosis cardiac sympathetic nerve activity increased progressively, leading to increased distal coronary resistance and lactate production, although the poststenotic vessels should be dilated fully by metabolic mechanisms, indicating that poststenotic vasodilatory reserve was impaired by sympathetic nerve activity. $*P < 0.05$ 20 min *v.* control (C); $\dagger P < 0.05$ 20 min *v.* 1 min. Data from Heusch and colleagues [29].

sympathomimetic-mediated vasoconstriction is prevented by this slow channel blocker. It is possible that this represents one mechanism which contributes to the cardioprotective effect of calcium-channel blockers. In an alternative approach, sympathetic blockade by thoracic extradural anaesthesia preserved poststenotic vascular reserve as demonstrated by Heusch and colleagues [29] (fig. 8).

These observations confirm the findings of Klassen and co-workers in 1980 [45]. They investigated the effect of thoracic extradural anaesthesia on the endocardial : epicardial ratio of blood flow distribution in the presence of myocardial infarction. As anticipated, infarction alone led to a preferential impairment of endocardial blood flow. During thoracic extradural blockade, redistribution of blood flow towards the endocardial layers was observed.

This observation was subsequently confirmed by Davis, DeBoer and Maroko [19] who induced sympathetic blockade by extradural thoracic blockade 1 h after occlusion of the LAD. They also measured regional myocardial blood flow with microspheres and demonstrated, in addition, that the endo : epi ratio was not improved by a decrease in epicardial blood flow but by an increase in endocardial blood flow. In this investigation two methods for assessment of infarct size were used: planimetry and tissue weight. Both methods led to the same results—the infarcted area 6 h after LAD occlusion was significantly lower in the group with extradural block. It is possible that sympathetic blockade may be of value for patients with ischaemic heart disease, but to date there is no clinical study which has examined this question and further experimental work is necessary to confirm these interesting findings.

The following statements may be made regarding laboratory studies directed towards improvement of myocardial oxygen demand : supply ratio during anaesthesia:

(1) Further studies are required on pharmacological approaches such as enhancement of

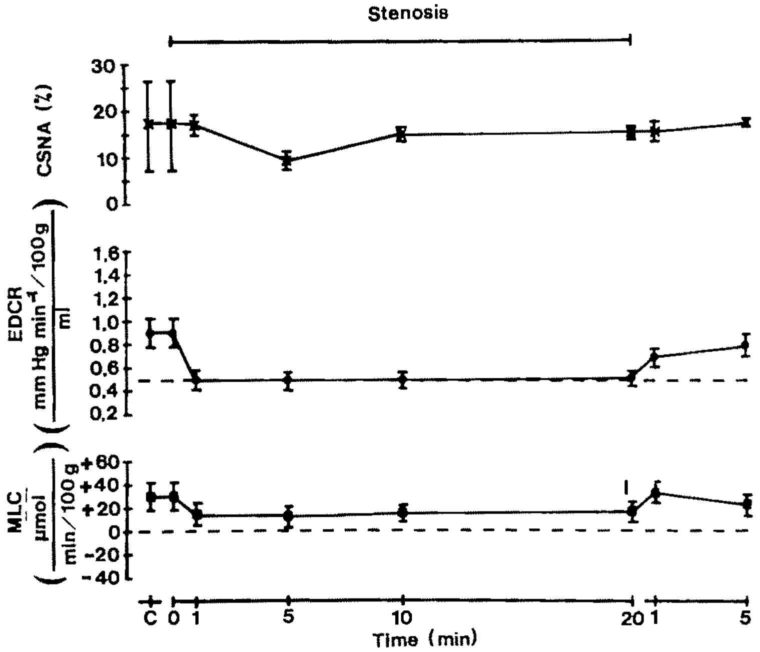


FIG. 8. The effects of 20 min of acute coronary stenosis on cardiac sympathetic nerve activity, distal coronary resistance and myocardial lactate consumption in six dogs following segmental extradural (C6–T6) anaesthesia with 2% procaine 1–3 ml. In contrast to similar experiments without thoracic extradural anaesthesia (see figure 7), no increase in sympathetic nerve activity and no increase in distal coronary resistance was observed and net lactate uptake was maintained. Data from Heusch and colleagues [29].

carbohydrate metabolism or improvement of poststenotic and collateral blood flow by inhibition of thromboxane formation.

(2) Poststenotic coronary blood flow is not dependent solely on perfusion pressure. There is evidence that sympathetic vasoconstriction may reduce poststenotic vasodilatory reserve.

(3) Sympathetic blockade by alpha-2 receptor blockers or thoracic extradural anaesthesia appears to restore poststenotic vasodilator reserve.

It is difficult to make clinical recommendations based upon laboratory studies. Because of anatomical species variation and the methods of producing ischaemia experimentally (particularly the lack of chronicity), it is not justifiable to extrapolate from laboratory data to the patient.

REFERENCES

1. van Ackern K, Adler M, Brückner UB, Buell U, Haller M, Mittmann U, Ragaller M, Raithel E, Vetter H, Wöllner W. Regional changes during myocardial ischemia: An animal experimental study. In: Peter K, Brown BR, Martin E, Norlander O, eds. *Inhalation Anesthetics*. Berlin, Heidelberg, New York, London, Tokyo: Springer-Verlag, 1986; 196–206.
2. van Ackern K, Vetter HO, Brückner UB, Mardler C, Mittman U, Peter K. Effects of enflurane on myocardial ischaemia in the dog. *British Journal of Anaesthesia* 1985; 57: 497–504.
3. Baller D, Bretschneider HJ, Hellige G. Validity of myocardial oxygen consumption parameters. *Clinical Cardiology* 1979; 2: 317–327.
4. Baller D, Sigmund-Duchanova H, Zipfel J, Hellige G. Prediction of myocardial blood flow by DPTI and prediction of the adequacy of myocardial O_2 supply by the DPTI–STTI ratio under maximal coronary dilation. *Basic Research in Cardiology* 1979; 74: 378–388.
5. Becker LC. Is isoflurane dangerous for the patient with coronary artery disease? *Anesthesiology* 1987; 66: 259–261.
6. Blanck JJ, Thompson M. Enflurane and isoflurane stimulate calcium transport by cardiac sarcoplasmatic reticulum. *Anesthesiology* 1982; 81: 142–145.
7. Bland JH, Lowenstein E. Halothane-induced decrease in experimental myocardial ischemia in the non-failing canine heart. *Anesthesiology* 1976; 45: 237.
8. Bosnjak ZJ, Kampine JP. Effects of halothane, enflurane and isoflurane on the SA node. *Anesthesiology* 1983; 58: 314–321.
9. Broadbent NP, Swan PC, Jones RM. Interactions between diltiazem and isoflurane. An *in vitro* investigation in isolated guineapig atria. *British Journal of Anaesthesia* 1985; 57: 1018–1021.
10. Brown BR, Crout JR. A comparative study of the effects of five general anesthetics on myocardial contractility. *Anesthesiology* 1971; 34: 236–245.

11. Buffington, CW, Romson JL, Levine A, Duttlinger NC, Huang AH. Isoflurane induces coronary steal in a canine model of chronic coronary occlusion. *Anesthesiology* 1987; **66**: 280–292.
12. Campus JH, Kapur PA. Combined effects of verapamil and isoflurane on coronary blood flow and myocardial metabolism. *Anesthesiology* 1982; **61**: A3.
13. Campus JH, Kapur PA. Combined effect of verapamil and isoflurane on coronary blood flow and myocardial metabolism in the dog. *Anesthesiology* 1986; **64**: 778–784.
14. Caplan RA, Su JY. Interaction of halothane and verapamil in isolated papillary muscle. *Anesthesia and Analgesia* 1986; **65**: 463–468.
15. Chelly JE, Rogers K, Hysing ES, Taylor A, Harley C, Merin RG. Cardiovascular effects of and interaction between calcium blocking drugs and anesthetics in chronically instrumented dogs. I. Verapamil and halothane. *Anesthesiology* 1986; **64**: 560–567.
16. Cocker S, Parratt JR, Ledingham IA, Zeitlin I. Thromboxane and prostacyclin release from ischaemic myocardium in relation to arrhythmias. *Nature (London)* 1981; **291**: 323–324.
17. Cocker S, Parratt JR. Effects of daxoziben on arrhythmias and ventricular fibrillation induced by coronary artery occlusion and reperfusion in anaesthetised greyhounds. *British Journal of Clinical Pharmacology* 1983; **15**: 87S–95S.
18. Conahan TJ, Blanck TJJ. Sarcoplasmatic reticulum: Enflurane effect on Ca dynamics. *Anesthesiology* 1979; **51**: S146.
19. Davis RF, de Boer LWV, Maroko PR. Thoracic epidural anesthesia reduces myocardial infarct size after coronary artery occlusion in dogs. *Anesthesia and Analgesia* 1986; **65**: 711–717.
20. Derfreyn G, Deckmyn H, Vermylen J. A thromboxane synthetase inhibitor reorients endoperoxide metabolism in whole blood towards prostacyline and prostaglandin E$_2$. *Thrombosis Research* 1982; **26**: 389–400.
21. Eger E. Isoflurane: A review. *Anesthesiology* 1981; **55**: 559–576.
22. Ellis EF, Oelz O, Roberts LJ, Payne NA, Sweetman BY, Nies AS, Oates JA. Coronary arterial smooth muscle contraction by a substance released from platelets: Evidence that it is thromboxane A$_2$. *Science* 1976; **193**: 1135–1137.
23. Ertl G, Simm F, Wichmann J, Fuchs M, Lochner W. The dependence of coronary collateral blood flow on regional vascular resistances. *Naunyn Schmiedebergs Archives of Pharmacology* 1979; **308**: 265–272.
24. Feigl EO. Coronary physiology. *Physiology Review* 1983; **63**: 1–205.
25. Gelman S, Fowler KC, Smith LR. Regional blood flow during isoflurane and halothane anesthesia. *Anesthesia and Analgesia* 1984; **63**: 557–565.
26. Goldberg AH, Ullrick WC. Effects of halothane on isometric contractions of isolated heart muscle. *Anesthesiology* 1967; **28**: 838–845.
27. Hattori Y, Azuma M, Gotoh Y, Kanno M. Negative inotropic effects of halothane, enflurane and isoflurane in papillary muscles from diabetic rats. *Anesthesia and Analgesia* 1987; **66**: 23–28.
28. Heusch G, Deussen A. The effects of cardiac sympathetic nerve stimulation on perfusion of stenotic coronary arteries in the dog. *Circulation Research* 1983; **53**: 8–15.
29. Heusch G, Duessen A, Thämer V. Cardiac sympathetic nerve activity and progressive vasoconstriction distal to coronary stenosis: feed-back aggravation of myocardial ischemia. *Journal of the Autonomic Nervous System* 1985; **13**: 311–326.
30. Hickey RF, Verrier ED, Baer RW, Vlahakes GJ, Fein G, Hoffman JIE. A canine model of acute coronary artery stenosis: Effects of deliberate hypotension. *Anesthesiology* 1983; **59**: 226–236.
31. Hirsh PD, Hillis LD, Campbell WD, Firth BG, Willerson JT. Release of prostacyclin and thromboxane into the coronary circulation in patients with ischemic heart disease. *New England Journal of Medicine* 1981; **304**: 685–691.
32. Hobbhahn J, Conzen P, Goetz A, Habazettl H, Granetzny T, Brendel W, Peter K. Blood flow and oxygen supply of the myocardium under isoflurane and enflurane. In: Peter K, Brown BR, Martin E, Norlander O, eds. *Inhalation Anaesthetics—New Aspects.* Berlin, Heidelberg, New York, London, Paris, Tokyo: Springer, 1986; 171–186.
33. Hoeft A, Korb H, Böck J, Wolpers HG, Wober W, Hellige G. Preservation of myocardium in transient ischemia by the thromboxane synthetase inhibitor UK 38.485. *Research in Experimental Medicine* 1986; **186**: 35–46.
34. Hoffman JIE, Buckberg GD. Myocardial supply: demand ratio—a critical review. *American Journal of Cardiology* 1978; **41**: 327–332.
35. Hysing E, Chelly JE, Doursout M-F, Hartley C, Merin RG. Cardiovascular effects of and interaction between calcium blocking drugs and anesthetics in chronically instrumented dogs. III. Nicardipin and isoflurane. *Anesthesiology* 1986; **65**: 385–391.
36. Kahles H, Mazger VA, Hellige G, Spiekermann PR, Bretschneider HJ. The influence of myocardial edema formation on the energy consumption of the heart during aerobiosis and hypoxia. *Basic Research in Cardiology* 1982; **77**: 158–163.
37. Kapur PA, Bloor BC, Flacke WE, Olewine SK. Comparison of cardiovascular responses to verapamil during enflurane, isoflurane and halothane anesthesia in the dog. *Anesthesiology* 1984; **61**: 156–160.
38. Kapur PA, Campus JH, Tippit SE. Influence of diltiazem and cardiovascular function and coronary hemodynamics during isoflurane anesthesia in the dog: Correlation with plasma diltiazem levels. *Anesthesia and Analgesia* 1986; **65**: 81–87.
39. Kapur PA, Matarazzo DA, Fung DM, Sullivan KB. The cardiovascular and adrenergic actions of verapamil or diltiazem in combination with propanolol during halothane anesthesia in the dog. *Anesthesiology* 1987; **66**: 122–129.
40. Kates RA, Kaplan JA, Guyton RA, Dorsey L, Hug CC, Hatcher CR. Hemodynamic interactions of verapamil and isoflurane. *Anesthesiology* 1983; **59**: 132–138.
41. Kates RA, Zaggy AP, Norfleet EA, Heath KR. Comparative cardiovascular effects of verapamil, nifedipine and diltiazem during halothane anesthesia in swine. *Anesthesiology* 1984; **61**: 10–18.
42. Kemmotsu O, Hashimoto Y, Shimosato S. Inotropic effects of isoflurane on mechanics of contraction in isolated cat papillary muscle from normal and failing hearts. *Anesthesiology* 1974; **39**: 470–477.
43. Kemmotsu O, Hashimoto Y, Shimosato S. The effects of

fluroxene and enflurane on contractile performance of isolated papillary muscle from failing hearts. *Anesthesiology* 1974; 40: 252–260.

44. Kettler D. *Sauerstoffbedarf und Sauerstoffversorgung des Herzens in Narkose.* Berlin, Heidelberg, New York: Springer-Verlag, 1973.
45. Klassen GA, Bramwell RS, Bromage PR, Zborowska-Sluis DT. The effect of acute sympathectomy by epidural anesthesia on the canine coronary circulation. *Anesthesiology* 1980; 52: 8–15.
46. Komai H, Rusy BF. Differences in the myocardial depressant action of thiopental and halothane. *Anesthesia and Analgesia* 1984; 63: 313–318.
47. Korb H, Hoeft A, Hunneman DH, Schraeder R, Wolpers HG, Wober W, Hellige G. Changes in myocardial substrate utilisation and protection of ischemic stressed myocardium by oxfenicine [(S)-4-hydroxyphenylglycine]. *Naunyn-Schmiedeberg's Archives of Pharmacology* 1984; 327: 70–74.
48. Lowenstein E, Foëx P, Francis CM, Davies WL, Yusuf S, Ryder WA. Regional ischemic ventricular dysfunction in myocardium supplied by a narrowed coronary artery with increasing halothane concentrations in the dog. *Anesthesiology* 1981; 55: 349.
49. Lowenstein E, Hill RD, Rjagopalan DP, Schneider RC. Winnie the Pooh revisited, or, the more recent adventures of the piglet. *Anesthesiology* 1982; 56: 81–83.
50. Lynch C. Are volatile anesthetics really calcium entry blockers? *Anesthesiology* 1984; 61: 644–646.
51. Lynch C. Differential depression of myocardial contractility by halothane and isoflurane *in vitro*. *Anesthesiology* 1986; 64: 620–631.
52. Lynch C, Vogel S, Pratila MD, Sperelakis N. Enflurane depression of myocardial slow action potentials. *Journal of Pharmacology and Experimental Therapeutics* 1982; 222: 405–409.
53. Lynch C, Vogel S, Sperelakis N. Halothane depression of myocardial slow action potentials. *Anesthesiology* 1981; 55: 360–368.
54. Mahaffey JE, Aldinger EE, Spronse JH, Darby TD, Thrower WB. The cardiovascular effects of halothane. *Anesthesiology* 1961; 22: 982–986.
55. Marshall AG, Kissin I, Reeves JG, Bradley EL, Blackstone UH. Interaction between negative inotropic effects on halothane and nifedipine in isolated rat heart. *Journal of Cardiovascular Pharmacology* 1983; 5: 592–597.
56. Mayer N, Steinbereithner K, Zimpfer M. Effects of halothane on the contractile performance of myocardium supplied by a chronically narrowed coronary artery in the dog. *Anesthesiology* (in press).
57. Mayer N, Zimpfer M. Einfluss von Enflurane auf die Funktion chronisch ischämischen Myokards. *Anaesthesist* 1985; 34: 556–562.
58. Medical Research Council: Clinical trial of potassium–glucose–insulin treatment in acute myocardial infarction. *Lancet* 1968; 2: 1355–1360.
59. Mergner GW, Gilman RW, Woolf WA, Patch JH. Effect of halothane and fentanyl on myocardial infarct size and regional blood flow distribution. *Anesthesiology* 1982; 57: A17.
60. Merin RG. Are the myocardial functional and metabolic effects of isoflurane really different from those of halothane? *Anesthesiology* 1981; 55: 398–408.
61. Merin RG. Slow channel inhibitors, anesthetics and cardiovascular function. *Anesthesiology* 1981; 55: 198–200.
62. Merin RG. Calcium channel blocking drugs and anesthetics: Is the drug interaction beneficial or detrimental? *Anesthesiology* 1987; 66: 111–113.
63. Merin RG, Chelly JE, Hysing ES, Rogers K, Delwati A, Hartley CJ, Abernethy DR, Doursout M-F. Cardiovascular effects of and interaction between calcium blocking drugs and anesthetics in chronically instrumented dogs. IV. Chronically administered oral verapamil and halothane, enflurane and isoflurane. *Anesthesiology* 1987; 66: 140–146.
64. Merin RG, Kumazawa T, Luka NL. Myocardial function and metabolism in the conscious dog during halothane anesthesia. *Anesthesiology* 1976; 44: 401–423.
65. Merin R, Kumazawa T, Luka NL. Enflurane depresses myocardial function, perfusion and metabolism in the dog. *Anesthesiology* 1976; 45: 501–507.
66. Merin RG, Verdouw PD, De Jong JW. Dose-dependent depression of cardiac function and metabolism by halothane in swine. *Anesthesiology* 1977; 46: 417–423.
67. Opie LH. The glucose hypothesis: Relation to acute myocardial ischemia. *Journal of Molecular and Cellular Cardiology* 1970; 1: 107–115.
68. Priebe HJ, Foëx P. Isoflurane causes regional myocardial dysfunction in dogs with coronary artery stenosis. *Anesthesiology* 1987; 66: 293–300.
69. Priebe HJ, Skarvan K. Cardiovascular and electrophysiologic interactions between diltiazem and isoflurane in the dog. *Anesthesiology* 1987; 66: 114–121.
70. Prys-Roberts C, Roberts JG, Foëx P, Clarke TNS, Bennett MJ, Ryder WA. Interactions of anesthesia beta-receptor blockade and blood loss in dogs with induced myocardial infarction. *Anesthesiology* 1976; 45: 326–339.
71. Ramsay JG, Cutfield GR, Francis CM, Delvin WH, Foëx P. Halothane–verapamil causes regional myocardial dysfunction in the dog. *British Journal of Anaesthesia* 1986; 58: 321–326.
72. Robertson RM, Robertson D, Roberts J. Thromboxane A_2 in vasotonic angina pectoris. Evidence from direct measurements and inhibitor trials. *New England Journal of Medicine* 1981; 304: 998–1003.
73. Schaper W, Flameng W, Winkler B, Wüsten B, Türschmann W, Neugebauer G, Carl M, Pasyk S. Quantification of collateral resistance in acute and chronic experimental coronary occlusion in the dog. *Circulation Research* 1976; 39: 371–377.
74. Shimosato S, Sugai N, Iwatsuki N, Etsten BE. The effect of ethrane on cardiac muscle mechanics. *Anesthesiology* 1969; 30: 513–518.
75. Sill JC, Bove AA, Nugent M, Blaise GA, Dewey JD, Grabau C. Effects of isoflurane on coronary arteries and coronary arterioles in the intact dog. *Anesthesiology* 1987; 66: 273–270.
76. Skarvan K, Priebe HJ, Gale J. Effects of diltiazem and isoflurane on cardiovascular function and coronary hemodynamics. *Anesthesiology* 1984; 61: A9.
77. Smith G, Evans DH, Asher MJ, Bentley S. Enflurane improves the oxygen supply/demand balance in the acutely ischaemic canine myocardium. *Acta Anaesthesiologica Scandinavica* 1982; 26: 44–47.
78. Smith G, Rogers K, Thorburn J. Halothane improves the balance of oxygen supply to demand in acute myocardial

ischaemia. *British Journal of Anaesthesia* 1980; **52**: 577–583.

79. Sodi-Pallares D, Testelli MR, Fishleder BL. Effects of an intravenous infusion of a potassium–glucose–insulin solution on the electrocardiographic signs of myocardial infarction. A preliminary clinical report. *American Journal of Physiology* 1962; **9**: 166–181.
80. Strauer BE. Contractile responses to morphine, piritramide, meperdine and fentanyl: A comparative study of effects on the isolated ventricular myocardium. *Anesthesiology* 1972; **37**: 304–310.
81. Su JY, Bell JG. Intracellular mechanism of action of isoflurane and halothane on striated muscle of rabbit. *Anesthesia and Analgesia* 1986; **65**: 457–462.
82. Su JY, Kerrik GL. Effects of halothane on caffeine-induced tension transients in functionally skinned myocardial fibre. *Pflügers Archives* 1979; **380**: 29–34.
83. Tosone SR, Reves JG, Kissin I, Smith LR, Fornier SE. Hemodynamic response to nifedipine in dogs anesthetised with halothane. *Anesthesia and Analgesia* 1983; **59**: 903–908.
84. Verrier ED, Edelist G, Consigny PM, Robinson S, Hoffman JIE. Greater coronary vascular reserve in dogs anesthetised with halothane. *Anesthesiology* 1980; **53**: 445–459.
85. van der Vusse GJ, van Belle H, van Grevan W, Kruger R, Reneman RS. Acute effect of fentanyl on haemodynamics and myocardial carbohydrate utilisation and phosphate release during ischaemia. *British Journal of Anaesthesia* 1979; **51**: 927–935.
86. Zimpfer M, Gilly H, Krösl P, Schlag G, Steinbereithner K. Importance of myocardial loading conditions in determining the effects of enflurane on left ventricular function in the intact and isolated canine heart. *Anesthesiology* 1983; **58**:159–169.
87. Zimpfer M, Gilly H, Mayer N, Steinbereithner K. Effects of isoflurane on global and segmental left ventricular function in intact dogs with chronic myocardial ischemia. *Anesthesiology* 1983; **59**: A32.

Br. J. Anaesth. (1988), **61**, 68–84

MYOCARDIAL ISCHAEMIA ASSOCIATED WITH GENERAL ANAESTHESIA

A Review of Clinical Studies

S. REIZ

The incidence of perioperative myocardial ischaemia in patients with coronary artery disease, as reported in the literature, varies widely (tables I, II). Much of the confusion surrounding this issue can probably be related to differences in patient populations studied, study programmes and techniques used to establish ischaemia (table III). Until recently, efforts to avoid myocardial ischaemia concentrated primarily upon decreasing myocardial oxygen demand by controlling hypertension and tachycardia. It was accepted widely that a reduction of arterial pressure was safe in patients with coronary artery disease (CAD), provided the contractility of the heart, and hence oxygen consumption, were depressed proportionally by the anaesthetic agent [18]. More recently, it has been recognized that myocardial oxygenation may, under some circumstances, be impaired, despite apparently normal systemic haemodynamics. When the first reports of non-haemodynamically related myocardial ischaemia, associated with inhalation anaesthesia in man, appeared in 1983 [52], it was not surprising that these data stimulated many investigators [4, 36–39] and created the impetus for intense research in the field.

In the years that followed, researchers focused their interest on three main areas:

(1) Clinical and laboratory studies on the coronary haemodynamic effects of anaesthetic agents and techniques and their relation to myocardial ischaemia.

(2) Development of more sensitive techniques for detecting ischaemia in the operating room.

(3) Epidemiological studies aimed at defining the intraoperative risk factors predicting perioperative myocardial injury.

This review deals mainly with the first of these areas, with special emphasis being placed on the role of ischaemia without associated haemodynamic abnormalities, for example myocardial oxygen deprivation related to vasomotion.

EFFECTS OF ANAESTHETIC AGENTS UPON THE CORONARY CIRCULATION AND MYOCARDIAL OXYGENATION IN PATIENTS WITH CORONARY ARTERY DISEASE

Short-Acting I.V. Induction Agents and Sedatives

Barbiturates

Although the effects that sedatives and induction agents have on systemic haemodynamics in patients with coronary artery disease are well documented, only a few studies exist of their action upon the coronary circulation and myocardial oxygenation. In unpremedicated vascular surgical patients studied by Reiz and co-workers [49], thiopentone 6 mg kg^{-1} caused substantial declines in systemic arterial pressure (−27%) and systemic vascular resistance, with only a modest (10%) increase in heart rate. Coronary blood flow decreased in parallel with perfusion pressure. Myocardial oxygen consumption decreased (−39%) and myocardial oxygen balance was maintained, as judged from the ECG and lactate balance studies. These data contrast with findings by Sonntag and colleagues [62] in healthy subjects given thiopentone 5 mg kg^{-1}. They observed tachycardia, but little effect on arterial pressure or cardiac output. Myocardial blood flow increased to meet the increased demand for oxygen associated with the tachycardia. There are a number of possible reasons for the contrasting results when compared with those obtained in patients with coronary artery disease. Depressed baroreceptor function [6], beta-blockade and impaired left ventricular function with high endogenous sympathetic activity [14] are some of

---

SEBASTIAN REIZ, M.D., PH.D., Department of Anaesthesia, University of Umeå, S-901 87 Umeå, Sweden.

TABLE I. *Incidence of pre-bypass myocardial ischaemia in coronary artery surgery*

Source	*n*	Incidence (%) Pre-induction	Incidence (%) Total	Mode of detection
Wilkinson et al. (1981) [70]	26	27	62	2-lead ECG, lactate
Lieberman et al. (1983) [32]	30	NA	67	2-lead ECG
Slogoff and Keats (1985) [60]	1023	18	37	2-lead ECG
Slogoff and Keats (1986) [61]	495	26	55	2-lead ECG

TABLE II. *Incidence of myocardial ischaemia in vascular and other non-cardiac surgery*

	n	Incidence (%) Pre-induction	Incidence (%) Total	Mode of detection
Roy, Edelist and Gilbert (1979) [55]	29	NA	38	Multi-lead ECG
Coriat et al. (1982) [9]	50	NA	39	V5 ECG
Häggmark et al. (1987) [17]	61	13	74	12-lead ECG, CKG, lactate

TABLE III. *Incidence of intra-operative myocardial ischaemia in vascular surgery in relation to mode of detection. Data from Häggmark and colleagues [17]*

Mode of detection	Incidence of ischaemia (%)
Cardiokymography (wall function)	53
12-lead ECG	34
Lactate balance	20
Increased PCWP and abnormal wave form	23
All modalities	74

the more obvious causes. These factors, alone or in combination, may explain why patients with cardiac disease have greater decreases in systemic arterial pressure and minimal reflex tachycardia.

Preliminary results from patients with CAD studied by the group headed by Reiz provide further information on the effects of thiopentone on myocardial oxygenation and blood flow distribution. Three groups of patients, all with stable CAD, were studied: group I had normal left ventricular (LV) function (ejection fraction (EF) > 0.50) and no hypertension; group II had hypertension and normal LV function; group III had depressed LV function (EF < 0.40), but no hypertension. Patients were premedicated with morphine 200 $\mu g\,kg^{-1}$ and anaesthesia was induced with fentanyl 3 $\mu g\,kg^{-1}$ followed by a dose of thiopentone 2–4 $mg\,kg^{-1}$, adjusted to keep mean arterial pressure within 70% of the awake value. Neuromuscular blockade for intubation was provided with suxamethonium 1.5 $mg\,kg^{-1}$. Patients were studied up to 10 min after tracheal intubation, at which time all the circulatory effects of laryngoscopy and intubation had passed. By this time, neuromuscular blockade had been achieved using pancuronium bromide and patients' lungs were ventilated with 30% oxygen–70% nitrous oxide to maintain normocapnia. Systemic and regional coronary haemodynamics were measured before induction, immediately before laryngoscopy and 2 and 10 min after intubation. Myocardial ischaemia was assessed from myocardial lactate balance studies at the same intervals.

Before induction, hypertensive patients had higher mean arterial pressures and patients with decreased LV function higher pulmonary capillary wedge pressures (fig. 1). Following induction, all three groups demonstrated a comparable decline in systemic arterial pressure. However, the responses in heart rate and filling pressure were different: while patients in groups I and III demonstrated an increase in heart rate, which was most pronounced in group III, no change was seen in group II, probably because 88% were receiving chronic medication with beta-blockers. Filling pressure increased in group I, remained unchanged in group II and decreased progressively in patients with depressed LV function (group III), probably because of unloading of the left ventricle by a decreased impedance to left ventricular ejection. With induction of anaesthesia, the proportion of total coronary blood flow directed to the left ventricle remained constant in group I and II, but decreased initially in group III. Left ventricular ischaemia, made evident by lactate production, was observed at this time in

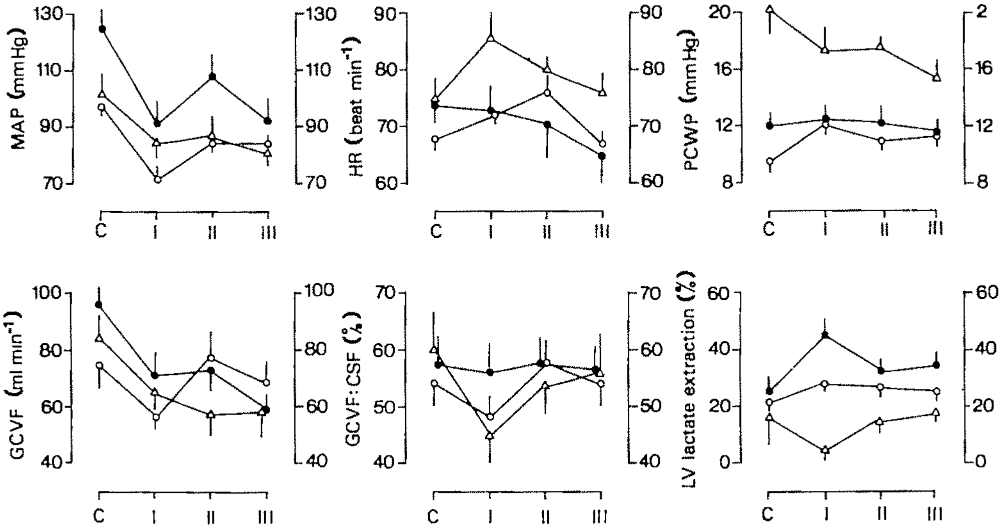


FIG. 1. Circulatory and cardiac metabolic effects of fentanyl–thiopentone induction and tracheal intubation in patients with coronary artery disease without complications (○), with hypertension (●) and with impaired left ventricular function (△). C = before induction; I = immediately before laryngoscopy; II, III = 2 and 10 min after intubation. MAP = mean arterial pressure; HR = heart rate; PCWP = pulmonary capillary wedge pressure; GCVF = great cardiac venous blood flow; CSF = total coronary sinus blood flow. Results are means ± SEM. For further details, see text.

approximately 33 % of the patients in group III, compared with 7 % and 6 % in groups I and II, respectively. These observations emphasize the importance of preventing even a moderate increase in heart rate (+15 %) and decline of coronary perfusion pressure (−17 %) in patients with high coronary back pressures.

Ketamine

Ketamine 2 mg kg^{-1} administered as the induction agent in patients with generalized atherosclerotic disease caused a transient increase in circulating plasma catecholamine concentrations, manifested by increases in systemic arterial pressure, heart rate, pulmonary capillary wedge pressure and systemic vascular resistance [3]. Both coronary blood flow and myocardial oxygen consumption increased by approximately 50 %, and myocardial oxygenation was adequate as judged by myocardial lactate metabolism and ECG.

Propofol

Stephan and colleagues [65] studied the systemic and coronary haemodynamic effects of propofol, administered as a bolus (2 mg kg^{-1}) followed by a continuous infusion (200 µg kg^{-1} min^{-1}) for induction of anaesthesia for coronary artery bypass grafting (CABG) in individuals with normal LV function. Before sternotomy, fentanyl 10 µg kg^{-1} was administered and patients' lungs were ventilated with 70 % nitrous oxide in oxygen. Induction of anaesthesia produced a variable, and sometimes pronounced, decline in coronary perfusion pressure, previously described by other investigators in similar patients [47]. Cardiac output decreased by a moderate extent and there was a slight increase in heart rate. Myocardial blood flow decreased in proportion to myocardial oxygen consumption. Myocardial ischaemia, as indicated by lactate production, developed in one of 12 patients, probably as a result of hypotension. Sternotomy was followed by normalization of all systemic haemodynamic variables with the exception of cardiac output. Myocardial lactate production associated with coronary vasospasm was observed in another patient.

Benzodiazepines

A large number of studies report minor systemic haemodynamic effects of various benzodiazepines used for induction or maintenance of anaesthesia in patients with cardiac disease [2, 25, 31, 34, 54, 58]. Studies of the action of these drugs upon the coronary circulation and myocardial oxygenation in such patients are, however, restricted to the cardiac catheterization laboratory. Diazepam produces minor changes in coronary blood flow. A slight coronary vasodilating action has been proposed [1, 10]. In patients with CAD, flunitrazepam 15 $\mu g\ kg^{-1}$ produced decreases in coronary perfusion pressure and left ventricular end-diastolic pressure and increases in heart rate and left ventricular $\dot{V}_{max}$. Despite a reduction in myocardial oxygen consumption, coronary blood flow remained unchanged and myocardial oxygen extraction declined [45]. These findings demonstrate that flunitrazepam has a coronary vasodilating action unrelated to changes in myocardial oxygen demand. However, none of the patients studied had ECG or metabolic evidence of ischaemia.

More recently, the same group of investigators [35] published data obtained under comparable conditions during cardiac catheterization in similar patients administered midazolam 0.2 $\mu g\ kg^{-1}$ i.v. Five to 15 min after this drug, coronary blood flow had decreased in proportion to the decline in myocardial oxygen consumption. The investigators observed a slight increase in coronary venous oxygen saturation, indicating some coronary vasodilatation. As in their previous study on flunitrazepam, no ischaemia was observed following the administration of midazolam.

In summary, short-acting drugs used for induction of anaesthesia or sedation have little or no direct effect on coronary vascular tone. Myocardial oxygenation is adequate, provided coronary perfusion pressure is controlled and tachycardia can be avoided. Ischaemia related to stress-induced coronary vasomotion is probably not prevented by these drugs (for further data, see below).

Inhalation Agents

Halothane

In one of few randomized studies, Wilkinson and colleagues [70] investigated the effects of 0.2–1 % end-tidal halothane or morphine 2 $mg\ kg^{-1}$ i.v. plus 50 % nitrous oxide in oxygen in patients undergoing CABG. Before surgical intervention, both techniques resulted in an approximately 20 % reduction in myocardial oxygen consumption. Coronary perfusion pressure was preserved better with morphine than during halothane anaesthesia. Halothane, but not morphine anaesthesia, was associated with a reduction in myocardial oxygen extraction, suggesting coronary vasodilatation. One patient in the halothane group had myocardial lactate production before induction of anaesthesia, whereas lactate production was observed in three patients after intubation. Three morphine patients had myocardial lactate production before anaesthesia, which changed to lactate uptake after intubation. These coronary haemodynamic effects of halothane are in agreement with work in healthy individuals receiving halothane–air–oxygen [64], in vascular surgical patients with a history of congestive heart failure and who received halothane–air–oxygen [50] and in patients with CAD and normal LV function who were given halothane–oxygen with and without nitrous oxide [44]. All four studies demonstrate increased coronary venous saturation during administration of halothane. One additional study performed in patients with stable CAD has documented similar changes in coronary perfusion pressure and myocardial oxygen consumption, without evidence of coronary vasodilatation during halothane anaesthesia [22].

Halothane produces a similar degree of coronary vasodilatation in the experimental animal [12, 66, 67]. Other animal studies have demonstrated that myocardial ischaemia associated with halothane anaesthesia appears to be a hydraulic phenomenon produced by decreased perfusion pressure rather than impairment of coronary autoregulation [7, 13].

In summary, the possible mild coronary vasodilatating action of halothane observed in humans appears to have little, if any, importance in the development of inadequate myocardial oxygenation, compared with the effects of altered systemic circulation.

Enflurane

Studies in the intact dog have demonstrated that enflurane dilates coronary vessels and that its vasodilating potency is greater than that of halothane [66, 67] (fig. 2). Heikkilä and coworkers [20] administered enflurane to patients during CABG. Induction of anaesthesia was accomplished with lorazepam–fentanyl–pancuronium and enflurane was delivered in 40 % oxygen in air. Enflurane did not decrease coronary blood flow as much as was expected from the decline in myocardial oxygen consumption. Hence, myocardial oxygen extraction was reduced. Similar observations were made in comparable patients by Moffitt and colleagues [41] and in vascular

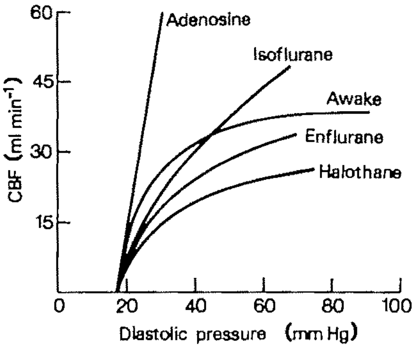


FIG. 2. Diastolic pressure–coronary flow relations in the awake and anaesthetized dog. Enflurane and isoflurane are more powerful coronary vasodilators than halothane, although none impairs coronary autoregulation comparably to adenosine. (Reproduced from Sybert and colleagues [66].)

surgical patients with CAD by Rydvall and associates [56]. These investigators also studied the regional coronary haemodynamic effects of enflurane by the use of the multiple thermistor, retrograde thermodilution coronary flow technique [48], allowing great cardiac venous blood flow (GCVF), which represents most of left ventricular blood flow, and total coronary sinus blood flow (CSF) to be assessed separately. The authors found a decline in the GCVF:CSF ratio from a mean of 0.70 to 0.54 following administration of 1 MAC enflurane. The results demonstrate a normal adjustment of the distribution of coronary blood flow to the decrease in regional myocardial oxygen consumption and thereby contradict the presence of any major regional maldistribution of coronary flow during enflurane anaesthesia.

Isoflurane

Animal experimentation has demonstrated that isoflurane, in common with adenosine and dipyridamole, dilates epicardial resistance vessels [59]. It is a weaker coronary vasodilator than adenosine (fig. 2) and dipyridamole, but has a considerably stronger coronary vasodilating action than halothane or enflurane [66, 67]. A similar relationship appears to exist in patients with CAD.

Reiz and colleagues [52] studied unpremedicated vascular surgical patients administered 1 MAC isoflurane in oxygen-enriched air (30:70). The anaesthetic was associated with a 35% reduction in coronary perfusion pressure, unchanged pulmonary capillary wedge pressure and a small increase in heart rate (+5 beat min^{-1}). Coronary blood flow remained unaltered, despite a 36% reduction in myocardial oxygen consumption. Myocardial oxygen extraction decreased from a mean of 68% to 48%. Similar systemic and coronary haemodynamic effects of isoflurane were observed in patients anaesthetized for CABG by Moffitt and colleagues [40]. Eleven of the 21 patients studied by Reiz had ECG or metabolic evidence of myocardial ischaemia. In 10 of the 21 patients, five of whom had evidence of ischaemia, coronary perfusion pressure was adjusted back to awake values by the use of i.v. infusions of phenylephrine and nitroglycerin. Heart rate was controlled to awake values using pacing electrodes incorporated in the coronary sinus catheter. Despite normalization of systemic haemodynamics, myocardial oxygen extraction remained profoundly decreased, providing evidence of persistent coronary vasodilatation. Ischaemia disappeared in two patients, but remained until isoflurane was discontinued in the remaining three. The authors suggested that maldistribution of coronary blood flow ("coronary steal"), produced by the coronary vasodilating effect of isoflurane, might be the mechanism for ischaemia in these three individuals. It was suggested also that isoflurane might decrease coronary vasodilating reserve and therefore arterial pressure, filling pressure and heart rate should be more rigorously controlled in patients with CAD who were anaesthetized with isoflurane. The study by Moffitt and associates [40] reported myocardial lactate production in three of 11 patients during an isoflurane–oxygen anaesthetic for CABG, deep enough to reduce systolic arterial pressure by 30%. Previously, the same group of investigators, using the same end-points in similar patients, observed no instance of myocardial lactate production during either halothane–oxygen or enflurane–oxygen anaesthesia.

Coronary arteriolar dilators have the potential for causing myocardial ischaemia by a steal syndrome or, in the case of a severe single vessel narrowing, by endo-to-epicardial flow maldistribution. The anatomical basis for coronary steal was proposed by Becker [5]. A territory behind a complete occlusion, perfused via collaterals from a stenosed artery may be subject to hypoperfusion if a small coronary vessel dilator is administered (fig. 3). This occurs because collaterals are less responsive to vasodilator stimuli than normal coronary vessels [57]. An area distal to a critical stenosis in which the vasculature is

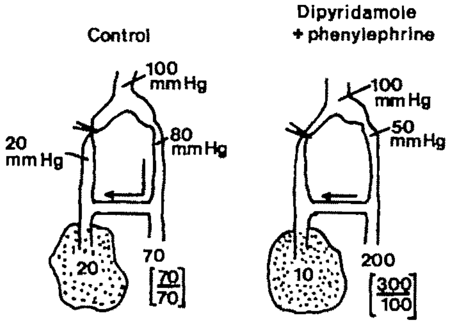


FIG. 3. Schematic diagram of the coronary circulation showing proposed mechanism for a vasodilator-induced coronary steal. The coronary artery divides into two branches, one completely occluded, and the other stenosed but providing collaterals to the first. In the control situation on the left, distal pressure is low in the occluded arterial bed and there is a small gradient in mean pressure across the stenosis. Flow in the ischaemic region (dotted area) is 20 ml $min^{-1}/100$ g and is determined by the collateral driving pressure, or the difference between distal pressures in the bed supplying collaterals (80 mm Hg) and the ischaemic bed (20 mm Hg). Flow in the distribution of the stenotic vessel is normal at 70 ml $min^{-1}/$ 100 g and is evenly distributed between subendocardium (lower value in bracket) and subepicardium (upper value). During dipyridamole administration, with arterial pressure maintained constant by phenylephrine, flow increases in the non-ischaemic bed to 200 ml $min^{-1}/100$ g, but becomes maldistributed between subendocardium and subepicardium. In addition, pressure distal to the stenosis decreases to 50 mm Hg, causing a reduction in collateral driving pressure. As a result, flow to the ischaemic region decreases to 10 ml $min^{-1}/$ 100 g, interpreted as a coronary steal. (Reproduced from Becker [5].)

maximally dilated and the autoregulatory reserve is exhausted may also be deprived of adequate blood flow when normal coronary vessels are dilated pharmacologically. Under these conditions, a small vessel coronary dilator may decrease flow through the collaterals or across the constriction, and flow may actually reverse from the area previously maximally dilated to the areas supplied by those vessels which are responsive to the vasodilator [69]. Intramyocardial blood flow maldistribution was demonstrated during exercise by Gallagher and colleagues [15] in dogs with chronic severe stenosis of a single coronary artery. Myocardial function and flow distribution were normal at rest but, during exercise, total flow to the stenotic segment remained unaltered instead of demonstrating the normal doubling. While flow to the subepicardium doubled normally, flow to the mid-myocardium remained unchanged and subendocardial blood flow approached zero. It has been proposed that an intervention which produces negative inotropy prevents maldistribution of myocardial blood flow in the presence of dilatation of both large and small coronary arteries [16]. This suggestion has to be considered when the possible role of isoflurane-associated myocardial ischaemia is discussed.

Larsen and colleagues [28] compared the systemic and coronary haemodynamic effects of enflurane and isoflurane administered in 50% nitrous oxide in oxygen for CABG in patients with normal LV function. Before sternotomy, the anaesthetic agents produced minimal and comparable systemic haemodynamic changes. Enflurane decreased myocardial blood flow more than isoflurane, and coronary sinus oxygen saturation was increased to the same degree. With sternotomy, important differences became apparent. In enflurane patients, myocardial blood flow increased and coronary sinus oxygen content decreased to meet the increased myocardial oxygen demand. In isoflurane patients, myocardial blood flow increased to the same degree as in enflurane patients, whereas coronary sinus oxygen saturation remained markedly increased, demonstrating persistent coronary vasodilatation and uncoupling of the normal autoregulatory response to increased demand for oxygen (fig. 4). None of the enflurane group exhibited evidence of myocardial ischaemia during the study period. Among isoflurane patients, one produced lactate before sternotomy and three thereafter.

Reiz and Östman [53] measured regional coronary blood flow during isoflurane–nitrous oxide anaesthesia for vascular surgery in patients with CAD. In approximately 50% of the patients, they found that isoflurane increased the GCVF:CSF ratio, despite markedly decreasing left ventricular oxygen consumption. A majority of these patients also had electrocardiographic or metabolic evidence of myocardial ischaemia. Khambatta and co-workers [26] compared the regional coronary haemodynamic effects of halothane and isoflurane in patients anaesthetized for CABG. They also measured the GCVF:CSF ratio, and found indications of coronary blood flow maldistribution in patients anaesthetized with isoflurane, but not with halothane. Four of 10 isoflurane patients, compared with none of the halothane patients, demonstrated metabolic evidence of ischaemia at comparable coronary perfusion pressures.

In a randomized trial, Hohner and colleagues [24] compared the effects of fentanyl 10 $\mu g\ kg^{-1}$, halothane and isoflurane in 60% nitrous oxide in oxygen, after induction of anaesthesia using fentanyl 3 $\mu g\ kg^{-1}$–thiopentone 2–4 $mg\ kg^{-1}$, on

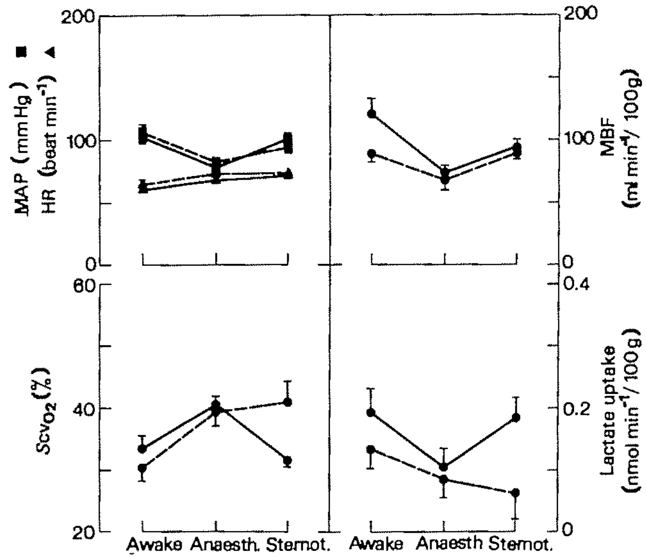


FIG. 4. Effects of anaesthesia and sternotomy on haemodynamics, myocardial blood flow (MBF) and lactate uptake and coronary venous oxygen saturation (Scv_{O_2}) in patients with coronary artery disease during inhaltion of enflurane (——) or isoflurane (----) with 50% nitrous oxide ($n = 10$ in each group). Note the difference in coronary venous oxygen saturation during surgery, suggesting persistent coronary vasodilatation in isoflurane-anaesthetized patients. (Plotted from data by Larsen and colleagues [28], with permission.)

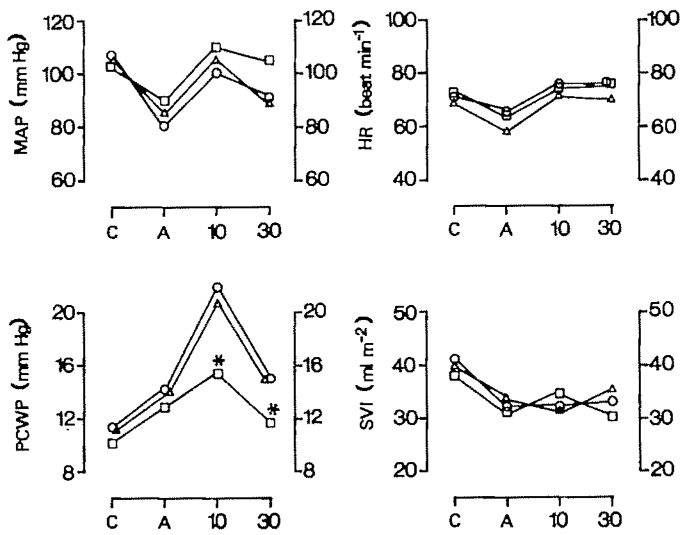


FIG. 5. Effects of halothane(○)-, isoflurane(△)- and fentanyl(□)-nitrous oxide-oxygen anaesthesia on mean arterial pressure (MAP), heart rate (HR), pulmonary capillary wedge pressure (PCWP) and stroke volume index (SVI) before (C) and during anaesthesia for major vascular surgical procedures. A = Steady state anaesthesia; 10 and 30 = 10 and 30 min after abdominal incision. Vasopressors and vasodilators were used to control systemic haemodynamics. With the exception of PCWP, which was significantly higher in the inhalation groups during surgery, haemodynamics in the three groups were indistinguishable. $^*P < 0.05$. (Replotted from data by Hohner and colleagues [24].)

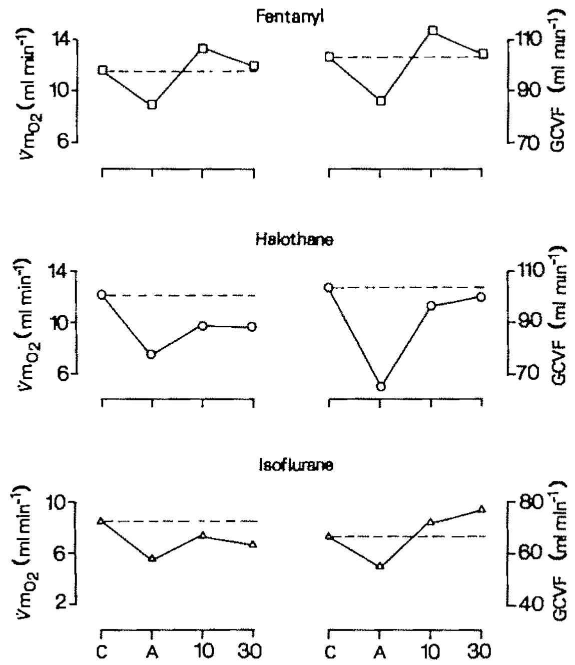


FIG. 6. Relationship between mean myocardial oxygen consumption ($\dot{V}mo_2$) (left panel) and mean coronary blood flow (right panel) in the corresponding territory during fentanyl (□)-, halothane(○)- and isoflurane(△)-nitrous oxide-oxygen anaesthesia (top to bottom) in vascular surgical patients. C = Awake; A = anaesthetized; 10, 30 = 10 and 30 min after abdominal incision. The results demonstrate that fentanyl does not dilate the coronary vasculature. Halothane is a mild and isoflurane a more powerful coronary vasodilator. (Replotted from data by Hohner and colleagues [24].)

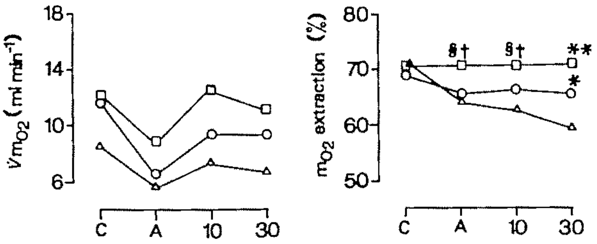


FIG. 7. Changes in mean myocardial oxygen consumption ($\dot{V}mo_2$) (left panel) and mean myocardial oxygen (mo_2) extraction (right panel) during fentanyl(□)-, halothane(○)- and isoflurane(△)-nitrous oxide-oxygen anaesthesia in vascular surgical patients. Despite similar changes in oxygen consumption in the three groups, there was a progressive decline in extraction in isoflurane patients. This indicates further coronary vasodilatation, probably related to increasing anaesthetic dose during surgery. C = Awake; A = anaesthetized; 10, 30 = 10 and 30 min after abdominal incision. Compared with isoflurane: $*P < 0.05$; $§P < 0.02$; $**P < 0.01$. Compared with halothane: $\dagger P < 0.05$. (Replotted from data by Hohner and colleagues [24].)

systemic and regional coronary haemodynamics and myocardial oxygenation. Pancuronium bromide was used for neuromuscular blockade. Halothane and isoflurane were administered according to a double-blind procedure. Systemic haemodynamics were maintained by adjustment of anaesthetic dose, pharmacological intervention, or both, to avoid hypotension, hypertension, tachycardia and failure. With the inclusion of the pharmacological intervention agents (phenylephrine and nitroglycerin), the effects of the three anaesthetics as regards to mean arterial pressure, heart rate and stroke volume were indistinguishable. Filling pressure during surgery was significantly less in fentanyl patients (fig. 5). Fentanyl did not affect coronary vascular tone, whereas halothane produced slight, and isoflurane more powerful and progressive, coronary vasodilatation despite comparable changes in myocardial oxygen consumption in the three groups (figs 6, 7). Myocardial ischaemia was assessed by a 12-lead ECG, cardiokymography, recording anterior left ventricular wall motion and myocardial lactate balance studies. Patients were ischaemic significantly more frequently in the inhalation groups (table IV). The total number of ischaemic episodes was greater in isoflurane-anaesthetized patients than in the halothane or fentanyl patients. This difference could partly be attributed to the increased coronary back pressure (e.g. pulmonary capillary wedge pressure) in the inhalation groups, and partly to significantly more ischaemic episodes without associated haemodynamic abnormalities in the isoflurane group (table IV). Six of the 14 isoflurane patients demonstrated one ischaemic episode each, which was not associated with tachycardia, hypertension, hypotension or failure. In a majority of these observations, and in contrast to patients anaesthetized with fentanyl or halothane, regional coronary blood flow measurements demonstrated uncoupling between coronary flow distribution and oxygen consumption in the corresponding territory (fig. 8).

All six clinical studies reported above support the concept of an isoflurane-associated redistribution of coronary blood flow as a cause of ischaemia. Three other studies in patients with CAD obtained data which have been interpreted to be in conflict with this suggestion. Hess and coworkers [21] used isoflurane to treat two patients with ischaemia which developed during sternotomy as a result of insufficient fentanyl-fluni-

TABLE IV. *Incidence of myocardial ischaemia in relation to haemodynamic abnormalities in patients anaesthetized with fentanyl-, halothane- or isoflurane–nitrous oxide for major vascular surgical procedures. Data from Hohner and colleagues [24].* **P < 0.05 compared with isoflurane if coronary vasospasm is excluded*; ***P < 0.02 compared with halothane and isoflurane*; ****P < 0.01 compared with isoflurane*

	Fentanyl (*n* = 10)	Halothane (*n* = 12)	Isoflurane (*n* = 14)
No. of ischaemic patients	2**	9	10
No. of ischaemic events	4***	12	19
With haemodynamic abnormalities	4	10	13
Without haemodynamic abnormalities	0*	2*	6
Coronary vasospasm	0	1	0
No. of ischaemic patients without haemodynamic abnormalities	0*	2*	6

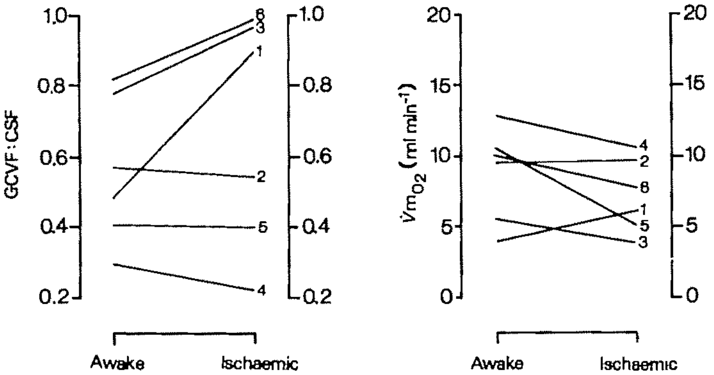


FIG. 8. Relation between oxygen consumption ($\dot{V}m_{O_2}$) in the LAD territory, drained by the great cardiac vein (GCV) (right panel) and the relative distribution of total coronary blood flow (CSF) to this area (GCVF:CSF) (left panel) in six isoflurane-anaesthetized patients with evidence of myocardial ischaemia without associated haemodynamic abnormalities. Decreased (patients Nos 3, 5, 6) or slightly increased (patient No. 1) oxygen consumption in four of the patients was not accompanied by proportional changes in blood flow distribution, indicating uncoupling of the association between flow and oxygen consumption and, probably, maldistribution of coronary blood flow. (Replotted from data by Hohner and colleagues [24].)

trazepam anaesthesia. Since coronary vasodilatation was probably maximal in the ischaemic area, the reduction in myocardial oxygen demand induced by isoflurane under these conditions must clearly have outweighed any adverse coronary redistributive effect of the anaesthetic agent. The data, however, do not permit any conclusions as regards the action of isoflurane upon coronary autoregulation.

O'Young and co-workers [46] investigated the regional coronary haemodynamic effects of isoflurane used to treat hypertension produced by sternotomy under high-dose sufentanil anaesthesia. Significant reductions of heart rate (−5%), mean arterial pressure (−25%), pulmonary capillary wedge pressure (−30%), systemic vascular resistance (−15%) and total and left ventricular oxygen consumption (−10% and −25%, respectively) were observed. The blood flow through the territories in which oxygen consumption was measured, however, was not significantly altered. Although the authors interpreted their data to indicate that autoregulation was not affected adversely by isoflurane, their results clearly demonstrate that the agent produced substantial coronary vasodilatation unrelated to changes in myocardial oxygen demand.

Tarnow and associates [68] investigated the effects of atrial pacing on the ECG V5 ST-segment before and during isoflurane–nitrous oxide anaesthesia in patients with CAD and normal LV function. When patients were paced during anaesthesia to the same heart rate that produced angina and significant ST-depression while awake, they had significantly less ST-

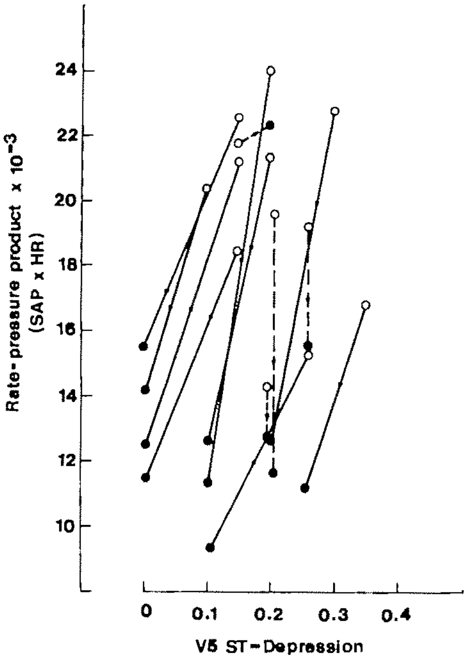


FIG. 9. Changes in rate–pressure product *v*. ST-segments with coronary artery disease awake (○) and anaesthetized with isoflurane–nitrous oxide (●). Anginal threshold was determined by atrial pacing while awake. The heart was then paced to the same heart rate during anaesthesia, at which time arterial pressure and filling pressures were lower than awake. Of 13 patients, three had unchanged ST-segments and one had more severe depression, despite decreased and unchanged oxygen demand respectively (broken lines). (Replotted from data by Tarnow and colleagues [68].)

depression. Furthermore, mean arterial pressure, pulmonary capillary wedge pressure and rate–pressure product (RPP) were lower than awake values. Although RPP has been demonstrated to be a poor indicator of myocardial oxygen consumption during anaesthesia [43], it is likely that myocardial oxygen consumption was reduced. This may explain the lesser ST-segment depression, provided that the degree of ST-depression was proportional to the metabolic severity of ischaemia. When individual data were analysed, isoflurane improved the tolerance to pacing-induced ischaemia in nine of 13 patients. However, three patients had unaltered ST-segment depression, despite pronounced reductions in RPP and one patient demonstrated further ST-depression with unaltered RPP (fig. 9). In these four patients with signs of impaired oxygen supply:demand ratio, we cannot exclude isoflurane-induced redistribution of myocardial blood flow as a factor contributing to worsening ischaemia.

Recent data collected by Hohner and colleagues [23] in vascular surgical patients with CAD suggest that isoflurane-associated coronary vasodilatation is dose-dependent. Coronary perfusion pressure and heart rate were controlled at near-awake values by pharmacological interventions for each dose range. When isoflurane was administered in concentrations less than 0.75 %, coronary vasodilatation was not observed. With increasing doses in the ranges 0.75–1.25 % and 1.5–2.0 %, there was a proportional decline in myocardial oxygen extraction, consistent with increasing coronary vasodilatation (fig. 10). It remains to be clarified if the incidence of isoflurane-associated myocardial ischaemia is also dose-related. The observations may explain why investigators who have used low doses of isoflurane as an adjunct to high-dose opioid anaesthesia in patients with CAD have been unable to document an increased incidence of ischaemia [46].

Evidence confirming the role of redistribution of coronary blood flow during isoflurane anaesthesia has been obtained more recently in animal models. Buffington and associates [8], in chronically instrumented dogs with the appropriate anatomical basis for a steal syndrome, demonstrated that 1 % isoflurane shifted myocardial blood flow from collateralized to normal myocardium. The maldistribution affected primarily the subendocardial zone and was associated with impaired wall function in the territory perfused by the collaterals. In comparison, halothane did not produce either redistribution of blood flow or impairment of wall function, despite a comparable effect on contractility.

Thus there is overwhelming experimental and clinical evidence that isoflurane, in common with other dilators of coronary resistance vessels, may cause ischaemia by maldistribution of myocardial blood flow, despite decreasing inotropy. Small coronary vessel dilators also reduce the tolerance to haemodynamic aberrations. It therefore appears prudent to maintain systemic haemodynamic values close to normal in patients with CAD if isoflurane is used in doses producing coronary vasodilatation. Nevertheless, it is likely that isoflurane at such doses could cause ischaemia by redistributing myocardial blood flow in patients with the appropriate anatomical basis for "coronary steal". Most probably, coronary vaso-

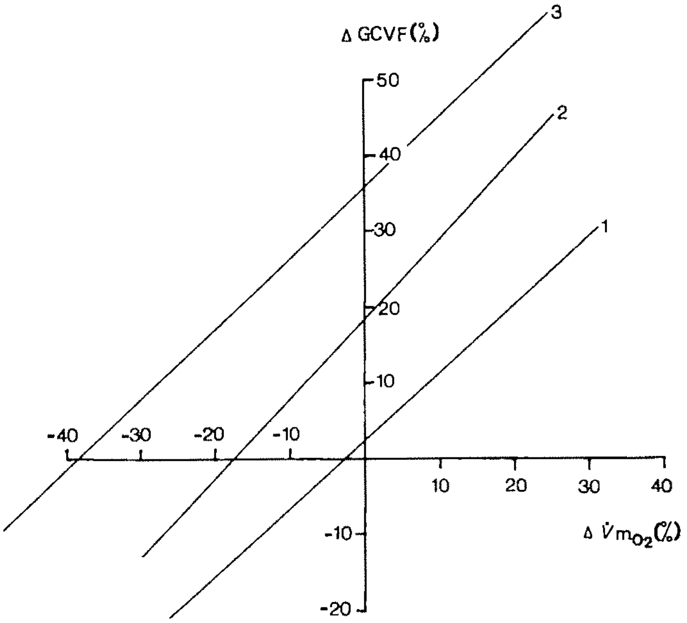


FIG. 10. Relation between changes in myocardial oxygen consumption (Δ$\dot{V}m_{O_2}$) and flow (ΔGCVF) in the corresponding territory with increasing isoflurane doses during anaesthesia for major vascular surgery. Regression lines: (1) 0.25–0.5 % Isoflurane: $y = 0.90x + 2.8$, $r = 0.957$, $n = 30$. (2) 0.75–1.25 % Isoflurane: $y = 1.03x + 19.1$, $r = 0.962$, $n = 33$. (3) 1.5–2.0 % Isoflurane: $y = 0.92x + 35.8$, $r = 0.925$, $n = 24$. The left-ward shift of the regression lines demonstrates greater coronary vasodilatation with higher doses of the anaesthetic agent. Isoflurane in concentrations less than 0.75 % does not produce coronary vasodilatation, since the regression line for the low concentration range (1) is not significantly different from the line of identity. (Data from Hohner and colleagues [23].)

dilatating doses of isoflurane should therefore be avoided in patients with CAD.

Nitrous oxide

Nitrous oxide constricts epicardial coronary arteries without affecting the resistance vessels in the intact dog [71]. In vascular surgical patients anaesthetized with enflurane, part exchange of enflurane for 70 % nitrous oxide, keeping MAC constant, resulted in further haemodynamic depression and distribution of regional coronary blood flow to awake patterns, despite a further decline in myocardial oxygen consumption [56]. Haemodynamic depression and increased myocardial oxygen extraction were noted also when 50 % nitrous oxide was added to enflurane or halothane anaesthesia for CABG [42, 44]. All these clinical data suggest that nitrous oxide may produce some coronary vasoconstriction. It remains to be clarified if this may modify the risk for myocardial ischaemia associated with coronary vasodilatation.

Opioids Used in Anaesthesia

Since high-dose opioid anaesthesia has become increasingly popular for heart surgery, many data on coronary haemodynamics and myocardial oxygenation with this technique have become available during recent years. Sonntag and coworkers studied patients with normal LV function during high-dose fentanyl anaesthesia for CABG [63]. After 10 μg kg^{-1}, minimal systemic haemodynamic changes were observed. After another 90 μg kg^{-1}, systemic haemodynamics were only marginally affected. Nevertheless, five of nine patients demonstrated myocardial lactate production. With sternotomy, mean heart rate increased by 22 beat min^{-1} and myocardial oxygen consumption by approximately 40 %. There was evidence of coronary vasodilatation and eight of the nine patients had metabolic evidence of myocardial ischaemia. In similar patients anaesthetized with a comparable total dose of fentanyl (75 μg kg^{-1} at induction and 25 μg kg^{-1} before sternotomy), Heikkilä and associates [20] found evidence of ischaemia after sternotomy in only one of 12 patients. In contrast to the patients investigated by Sonntag's group, surgery induced coronary vasoconstriction, as demonstrated by increased myocardial oxygen extraction and coronary vascular resistance. In another study by the same group of investigators [19], administration of droperidol before sternotomy inhibited the surgically induced coronary vasoconstriction without affecting the incidence of myocardial ischaemia. Part of the conflicting results in the studies by Sonntag and Heikkilä can probably be attributed to differences in the design of the studies. At the time of surgery, plasma concentrations of fentanyl were probably considerably higher in Heikkilä's patients, resulting in better systemic haemodynamic stability, and hence lower incidence of ischaemia.

Data from vascular surgical patients with CAD who received lower doses of fentanyl (10–15 $\mu g\ kg^{-1}$) with nitrous oxide after thiopentone induction [24, 51] have demonstrated that coronary autoregulation is well maintained. Surgical stimulation may produce coronary vasoconstriction and associated ischaemia. The incidence of myocardial ischaemia is comparable to that reported during high-dose fentanyl anaesthesia for CABG by Heikkilä and colleagues [19, 20].

OTHER FACTORS

Effects of interventions during anaesthesia

Laryngoscopy, endotracheal intubation and major surgical stimulation appear to have profound coronary flow limiting effects, thereby threatening myocardial oxygen delivery.

The group headed by Maseri has been at the forefront in establishing coronary vasospasm as an important mechanism of ischaemia in stable angina pectoris. Unlike classical variant angina, which presents with ST-segment elevation, coronary spasm may be associated also with pseudonormalization or depression of the ST-segments. Deanfield and associates [11] documented ST-depressions and temporally related impairment of coronary perfusion by scintigraphy after mental arithmetic in the absence of haemodynamic changes in patients with CAD. Frequently, these ischaemic episodes were not accompanied by angina pectoris.

Ischaemia before and during induction

The incidence of non-haemodynamically related new ischaemic ECG changes upon arrival in the operating room is reported to be of the order of 25% in patients scheduled for CABG (table I) [60, 61, 70]. Most commonly, the ischaemia was

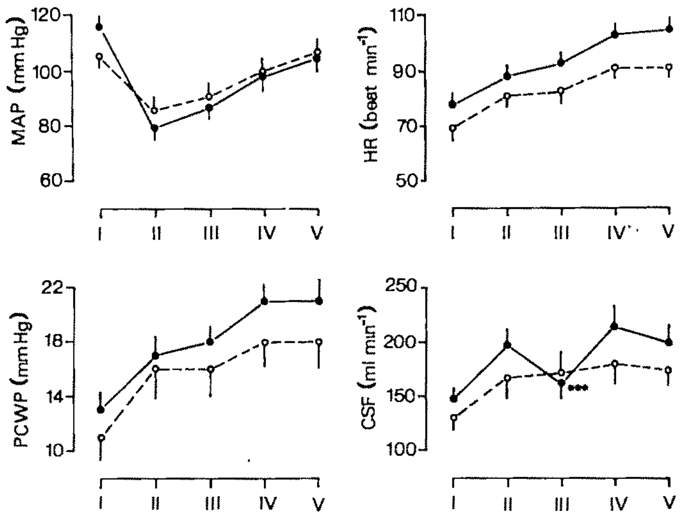


FIG. 11. Haemodynamics and coronary sinus blood flow (CSF) before, during and after laryngoscopy and intubation in 30 patients who became ischaemic (●——●) and 20 matched, non-ischaemic patients (○—○). Note the similarity of haemodynamic changes, but the transient decline in coronary sinus blood flow in patients who developed ischaemia. The data suggest that coronary vasospasm is involved. I = Awake; II = 5 s before laryngoscopy; III = laryngoscopy; IV = intubation ended; V = maximum haemodynamic changes. ***$P < 0.001$ compared with non-ischaemic patients from II to III. (Data from Lowenstein and Reiz [33], reproduced with permission.)

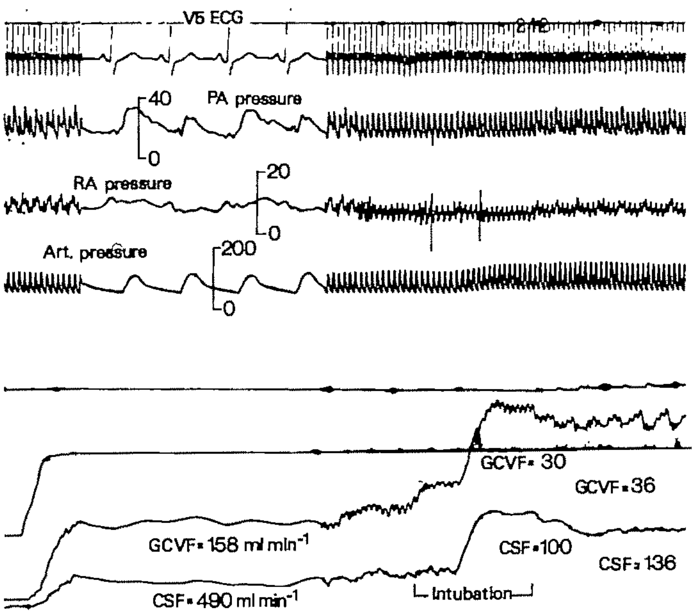


FIG. 12. ECG, haemodynamics and coronary blood flows (top to bottom) before, during and following laryngoscopy and tracheal intubation in a patient with coronary artery disease. Note the pronounced decline in both total (CSF) and LAD (GCVF) coronary blood flows initiated by the laryngoscopy, preceding any haemodynamic change. The time course suggests that the vasospasm is mediated neurogenically.

silent, that is, not associated with chest pain. During anaesthesia, the incidence of ischaemia reported in these patients was of the order of 20–40%. At least 50% of the ischaemic episodes were unrelated temporally to haemodynamic abnormalities, suggesting that disturbed vasomotion might have limited or maldistributed oxygen delivery.

Kleinman and associates [27] studied patients during tracheal intubation before CABG. Anaesthesia was induced with either halothane or high-dose fentanyl. Thallium scintigraphy revealed new myocardial perfusion defects in approximately 45% of patients in either group. These signs of relative, regional hypoperfusion were not associated with haemodynamic abnormalities and were accompanied only occasionally by ECG evidence of ischaemia. They suggest that tracheal intubation may elicit coronary vasospasm.

Similar results have been documented in vascular surgical patients with CAD, with the trachea intubated after induction with fentanyl–thiopentone, followed by either enflurane– or isoflurane–oxygen anaesthesia [33]. Thirty patients who developed electrocardiographic evidence of myocardial ischaemia following intubation were compared with 20 matched patients without ECG documented ischaemia at this time. Both groups had similar changes in systemic arterial pressure, heart rate and pulmonary capillary wedge pressure. Strikingly, patients with ischaemia had a transient decline in coronary blood flow immediately following laryngoscopy (fig. 11). The reduction in coronary blood flow preceded the changes in systemic haemodynamics (fig. 12). All these data suggest that coronary vasospasm might initiate myocardial ischaemia during laryngoscopy and tracheal intubation. The rapid decline of coronary blood flow, preceding the systemic haemodynamic changes suggests a neurogenic, rather than a humoral, mechanism of action.

Surgical stimulation

Several studies report coronary haemodynamic changes during surgical stimulation. The same lack of agreement between studies noted previously exists. The study by Wilkinson [70], comparing morphine– with halothane–nitrous oxide anaesthesia, found significant haemodynamic changes following sternotomy in both groups. Myocardial oxygenation was inadequate, as judged by lactate production or abnormalities

TABLE V. *Change in coronary blood flow distribution (GCVF:CSF) (from first value, to second value) in relation to changes in left ventricular oxygen consumption during fentanyl–, halothane– and isoflurane–nitrous oxide anaesthesia. With normal autoregulation, GCVF:CSF should decrease with a decline in oxygen consumption and increase when oxygen consumption is increased. The data demonstrate that isoflurane produces vasodilatation that is not related to changes in energy demand. Data from Hohner and colleagues* [24]

	Change in GCVF:CSF (from ... to ...)		
	Fentanyl	Halothane	Isoflurane
Myocardial oxygen consumption			
Increased	0.38±0.03 to 0.65±0.06 $P < 0.02$	0.44±0.05 to 0.68±0.04 $P < 0.05$	0.49±0.07 to 0.54±0.08 ns
Decreased	0.62±0.06 to 0.43±0.03 $P < 0.01$	0.65±0.05 to 0.49±0.06 ns	0.56±0.05 to 0.50±0.04 ns

in the ECG, in four of 12 morphine patients and in nine of 14 patients given halothane. Hilfiker and colleagues [22] investigated similar patients using halothane–nitrous oxide anaesthesia, but did not record any systemic or coronary haemodynamic changes following sternotomy, nor was ischaemia diagnosed in any patient.

The coronary haemodynamic effects of abdominal incision were also different between vascular surgical patients receiving halothane–, isoflurane– or fentanyl–nitrous oxide in oxygen anaesthesia in a randomized, partly double-blind study [24]. Pharmacological interventions were performed to counteract hypotension, hypertension and tachycardia. At 10 and 30 min after the incision, mean arterial pressure, heart rate and stroke volume index were comparable in the three groups. Pulmonary capillary wedge pressure was significantly higher in patients administered inhalation agents when compared with those receiving fentanyl (fig. 5). In fentanyl and halothane patients, coronary blood flow followed changes in myocardial oxygen consumption and myocardial oxygen extraction approached control values. In patients administered isoflurane, left ventricular oxygen extraction remained profoundly depressed during surgery, despite increasing demand for oxygen (figs 6, 7). These findings agree closely with those reported by Larsen and co-workers [29, 30], who studied the effects of enflurane– compared with isoflurane–nitrous oxide in oxygen anaesthesia in patients during myocardial revascularization (fig. 4). In patients anaesthetized with enflurane, myocardial blood flow and coronary sinus oxygen saturation decreased to meet the increased demand for oxygen induced by sternotomy. Patients anaesthetized with isoflurane demonstrated increased myocardial blood flow, whereas coronary venous oxygen saturation remained markedly increased with sternotomy. In the study of Hohner and colleagues [24], patients receiving fentanyl or halothane had a GCVF:CSF ratio which varied predictably with alterations in left ventricular oxygen consumption. In contrast, patients anaesthetized with isoflurane did not exhibit a change in this flow ratio, indicating uncoupling between coronary blood flow and myocardial oxygen consumption (table V).

In summary, vasoactive drugs administered as adjuncts to anaesthesia appear to interfere little with the action of general anaesthetic agents upon the coronary circulation. In contrast, laryngoscopy, tracheal intubation and the stress of surgery may elicit profoundly flow-limiting reactions in patients with CAD. During isoflurane anaesthesia, signs of coronary vasodilatation persist during surgery, despite clear evidence of myocardial oxygen deprivation. This indicates that hyper- and hypoperfusion may coexist during isoflurane anaesthesia.

ACKNOWLEDGEMENT

Supported in part by grants from the Swedish National Foundation against Heart and Lung Diseases.

REFERENCES

1. Abel RM, Reis RL, Staroscik RN. The pharmacological basis of coronary and systemic vasodilator actions of diazepam (Valium). *British Journal of Pharmacology* 1970; 39: 261–274.
2. Al-Khudhairi D, Whitwam JG, Chakrabarti MK, Askitopoulou H, Grundy EM, Powrie S. Haemodynamic effects of midazolam and thiopentone during induction of anaesthesia for coronary artery surgery. *British Journal of Anaesthesia* 1982; 54: 831–836.

3. Bålfors E, Häggmark S, Nyhman H, Rydvall A, Reiz S. Droperidol inhibits the effects of intravenous ketamine on central hemodynamics and myocardial oxygen consumption in patients with generalised atherosclerotic disease. *Anesthesia and Analgesia* 1983; **62**: 193–197.
4. Becker LC. Is isoflurane dangerous for the patient with coronary artery disease? *Anesthesiology* 1987; **66**: 259–261.
5. Becker LC. Conditions for vasodilator-induced coronary steal in experimental myocardial ischemia. *Circulation* 1978; **57**: 1103–1110.
6. Bristow JD, Prys-Roberts C, Fisher A, Pickering TG, Sleight P. Effects of anesthesia on baroflex control of heart rate in man. *Anesthesiology* 1969; **31**: 422–428.
7. Buffington CW. Impaired systolic thickening associated with halothane in the presence of a coronary stenosis is mediated by changes in hemodynamics. *Anesthesiology* 1986; **64**: 632–640.
8. Buffington CW, Fomson JL, Levine A, Duttlinger NC, Huang AH. Isoflurane induces coronary steal in a canine model of chronic coronary occlusion. *Anesthesiology* 1987; **66**: 280–292.
9. Coriat P, Harari A, Daloz M, Viars P. Clinical predictors of intraoperative myocardial ischaemia in patients with coronary artery disease undergoing non-cardiac surgery. *Acta Anaesthesiologica Scandinavica* 1982; **26**: 287–290.
10. Cote P, Gueret P, Bourassa MG. Systemic and coronary hemodynamic effects of diazepam in patients with normal and diseased coronary arteries. *Circulation* 1974; **50**: 1210–1216.
11. Deanfield JE, Maseri A, Selwyn AP, Ribeiro P, Chierchia S, Krikler S, Morgan M. Myocardial ischaemia during daily life in patients with stable angina: Its relation to symptoms and heart rate changes. *Lancet* 1983; **2**: 753–758.
12. Domenech RJ, Macho P, Valdes J, Penna M. Coronary vascular resistance during halothane anesthesia. *Anesthesiology* 1977; **46**: 236–240.
13. Francis CM, Foëx P, Lowenstein E, Glazebrook CW, Davies WL, Ryder WA, Jones LA. The interaction between regional myocardial ischaemia and left ventricular performance under halothane anaesthesia. *British Journal of Anaesthesia* 1982; **54**: 965–979.
14. Gaffney TE, Braunwald E. Importance of the adrenergic nervous system in support circulatory function in patients with congestive heart failure. *American Journal of Medicine* 1963; **34**: 320–324.
15. Gallagher KP, Osakada G, Matsuzaki M, Kemper WS, Ross J jr. Myocardial blood flow and function with critical coronary stenosis in exercising dogs. *American Journal of Physiology* 1982; **243**: H698–707.
16. Gewirtz H, Gross SL, Williams DO, Most AS. Contrasting effects of nifedipine and adenosine on regional myocardial blood flow distribution and metabolism distal to a severe coronary artery stenosis. Observations in sedated, closed chest domestic swine. *Circulation* 1984; **69**: 1048–1057.
17. Häggmark S, Hohner P, Johansson G, Ostman M, Friedman A, Diamond G, Lowenstein E, Reiz S. Comparison of hemodynamic, electrocardiographic, mechanical and metabolic indicators of intra-operative myocardial ischaemia in vascular surgical patients with coronary artery disease. *Anesthesiology*, (in press).
18. Hamilton WK. Do let the blood pressure drop and do use myocardial depressants! *Anesthesiology* 1976; **45**: 273–274.
19. Heikkilä H, Jalonen J, Arola M, Laaksonen V. Surgical stimulation during high-dose fentanyl anaesthesia: Effects of dehydrobenzperidol on the haemodynamics and myocardial oxygenation. *Acta Anaesthesiologica Scandinavica* 1985; **29**: 259–264.
20. Heikkilä H, Jalonen J, Arola M, Laaksonen V. Haemodynamics and myocardial oxygenation during anaesthesia for coronary artery surgery: Comparison between enflurane and high-dose fentanyl anaesthesia. *Acta Anaesthesiologica Scandinavica* 1985; **29**: 457–464.
21. Hess W, Arnold B, Schulte-Sasse U, Tarnow J. Comparison of isoflurane and halothane when used to control intraoperative hypertension in patients undergoing coronary artery bypass surgery. *Anesthesia and Analgesia* 1983; **62**: 15–20.
22. Hilfiker O, Larsen R, Sonntag H. Myocardial blood flow and oxygen consumption during halothane–nitrous oxide anaesthesia for coronary revascularization. *British Journal of Anaesthesia* 1983; **55**: 927–932.
23. Hohner P, Häggmark S, Johansson G, Nancarrow C, Reiz S. Dose-dependent coronary vasodilation by isoflurane in patients with coronary artery disease. *Anesthesiology* (in press).
24. Hohner P, Häggmark S, Johansson G, Reiz S. Mechanisms of myocardial ischaemia during anaesthesia. *Proceedings of the Swedish Society of Anaesthesiologists* (ISSN 0283–8818) 1987; **1**: A26.
25. Kawar P, Carson IW, Clarke RSJ, Dundee JW, Lyons SM. Haemodynamic changes during induction of anaesthesia with midazolam and diazepam (Valium) in patients undergoing coronary artery bypass surgery. *Anaesthesia* 1985; **40**: 767–771.
26. Khambatta HJ, Sonntag H, Larsen R, Stephan H, Stone JG, Kettler D. Coronary artery disease: global and regional myocardial blood flow and metabolism during equipotent halothane and isoflurane anesthesia. *Anesthesiology* 1986; **65**: A503.
27. Kleinman B, Henkin RE, Glisson SN, El-Etr AA, Bakhos M, Sullivan JH, Montoya A, Piffarre R. Qualitative evaluation of coronary flow during anesthetic induction using thallium-201 perfusion scans. *Anesthesiology* 1986; **64**: 157–164.
28. Larsen R, Hilfiker O, Merkel G, Sonntag H, Drobnik L. Myocardial oxygen balance during enflurane and isoflurane anesthesia for coronary artery surgery. *Anesthesiology* 1984; **61**: A4.
29. Larsen R, Hilfiker O, Philbin DM, Sonntag H. Isofluran: Koronardurchblutung und Myokardstoffwechsel bei Patienten mit koronarer Herzkarnkheit. *Anaesthesist* 1986; **35**: 284–290.
30. Larsen R, Hilfiker P, Philbin DM, Sonntag H. Koronardurchblutung, myokardialer Sauerstoffverbrauch und Myokardstoffwechsel unter Enfluran–Lachgas-Anaesthesie beim Koronarkranken. *Anaesthesist* 1986; **35**: 10–16.
31. Lepage J-Y, Blanloeil Y, Pinaud M, Helias J, Auneau C, Cozian A, Souron R. Hemodynamic effects of diazepam, flunitrazepam and midazolam in patients with ischemic heart disease: Assessment with a radionucleide approach. *Anesthesiology* 1986; **65**: 678–683.
32. Lieberman RW, Orkin FK, Jobes DR, Schwartz AJ. Hemodynamic predictors of myocardial ischemia during halothane anesthesia for coronary-artery revascularisation. *Anesthesiology* 1983; **59**: 36–41.
33. Lowenstein E, Reiz S. Effects of inhalation anesthetics on

systemic hemodynamics and the coronary circulation. In: Kaplan JA, ed. *Cardiac Anesthesia*. 2nd edn Vol. 1. 1987; 3–35.

34. McCannon RL, Hilgenberg JC, Stoelting RK. Hemodynamic effects of diazepam and diazepam–nitrous oxide in patients with coronary artery disease. *Anesthesia and Analgesia* 1980; **59**: 438–441.
35. Marty J, Nietenberg A, Blanchet F, Zouioueche S, Desmonts JM. Effects of midazolam on the coronary circulation in patients with coronary artery disease. *Anesthesiology* 1986; **64**: 206–210.
36. Merin RG. Is anesthesia beneficial for the ischemic heart? *Anesthesiology* 1980; **53**: 439–440.
37. Merin RG. Is anesthesia beneficial for the ischemic heart? II *Anesthesiology* 1981; **55**: 341–342.
38. Merin RG. Is isoflurane dangerous for the patient with coronary artery disease? Another view I. *Anesthesiology* 1987; **67**: 284–286.
39. Merin RG, Lowenstein E, Gelman S. Is anesthesia beneficial for the ischemic heart? III. *Anesthesiology* 1986; **64**: 137–140.
40. Moffitt EA, Barker RA, Glenn JJ, Imrie DD, DeCampo C, Landymore RW, Kinley CE, Murphy DA. Myocardial metabolism and hemodynamic responses with isoflurane anesthesia for coronary artery surgery. *Anesthesia and Analgesia* 1986; **65**: 53–61.
41. Moffitt EA, Imrie DD, Scovil JE, Glenn JJ, Cousins CL, DelCampo C, Sullivan JA, Kinley CE. Myocardial metabolism and hemodynamic responses with enflurane anaesthesia for coronary artery surgery. *Canadian Anaesthetists' Society Journal* 1984; **31**: 604–610.
42. Moffitt EA, Scovill JE, Barker RA, Imrie DD, Glenn JJ, Cousins CL, Sullivan JA, Kinley CE. The effects of nitrous oxide on myocardial metabolism and hemodynamics during fentanyl and enflurane anesthesia in patients with coronary disease. *Anesthesia and Analgesia* 1984; **63**: 1071–1075.
43. Moffitt EA, Sethna DH, Gray RJ, DeRobertis M, Matloff JM, Bussell JA. Rate–pressure product correlates poorly with myocardial oxygen consumption during anaesthesia in coronary patients. *Canadian Anaesthetists' Society Journal* 1984; **31**: 5–12.
44. Moffitt EA, Sethna DH, Gray R, Raymond MJ, Matloff JM, Bussell JA. Nitrous oxide added to halothane reduces coronary flow and myocardial oxygen consumption in patients with coronary disease. *Canadian Anaesthetists' Society Journal* 1983; **30**: 5–9.
45. Nitenberg A, Marty J, Blanchet S, Zouioueche S, Baury A, Desmonts JM. Effects of flunitrazepam on left ventricular performance, coronary haemodynamics and myocardial metabolism in patients with coronary artery disease. *British Journal of Anaesthesia* 1983; **55**: 1179–1184.
46. O'Young J, Mastrocostopoulos G, Hilgenberg A, Palacios I, Kyritsis A, Lappas DG. Myocardial circulatory and metabolic effects of isoflurane and sufentanil during coronary artery surgery. *Anesthesiology* 1987; **66**: 653–658.
47. Patrick MR, Blair IJ, Feneck RO, Sebel PS. A comparison of the haemodynamic effects of propofol (Diprivan) and thiopentone in patients with coronary artery disease. *Postgraduate Medical Journal* 1985; **61** (Suppl. 3): 23–27.
48. Pepine CJ, Mehta J, Webster W jr, Nichols WW. *In vivo* validation of a dilution method to determine regional left ventricular blood flow in patients with coronary disease. *Circulation* 1978; **58**: 795–802.
49. Reiz S, Bålfors E, Friedman A, Häggmark S, Peter T. Effects of thiopentone on cardiac performance, coronary haemodynamics and myocardial oxygen consumption in chronic ischaemic heart disease. *Acta Anaesthesiologica Scandinavica* 1981; **25**: 103–110.
50. Reiz S, Bålfors E, Gustavsson B, Häggmark S, Nath S, Rydvall A, Truedson H. Effects of halothane on coronary haemodynamics and myocardial metabolism in patients with ischaemic heart disease and heart failure. *Acta Anaesthesiologica Scandinavica* 1982; **26**: 133–138.
51. Reiz S, Bålfors E, Häggmark S, Nath S, Rydvall A, Truedson H. Myocardial oxygen consumption and coronary haemodynamics during fentanyl–droperidol–nitrous oxide anaesthesia in patients with ischaemic heart disease. *Acta Anaesthesiologica Scandinavica* 1981; **25**: 286–292.
52. Reiz S, Bålfors E, Sorensen MB, Ariola S jr, Friedman A, Truedson H. Isoflurane—a powerful coronary vasodilator in patients with coronary artery disease. *Anesthesiology* 1983; **59**: 91–97.
53. Reiz S, Östman M. Regional coronary hemodynamics during isoflurane–nitrous oxide anesthesia in patients with ischemic heart disease. *Anesthesia and Analgesia* 1985: **64**: 570–576.
54. Reves JG, Samuelson PN, Lewis S. Midazolam maleate induction in patients with ischaemic heart disease: haemodynamic observations. *Canadian Anaesthetists' Society Journal* 1979; **26**: 402–409.
55. Roy WL, Edelist G, Gilbert B. Myocardial ischemia during non-cardiac surgical procedures in patients with coronary-artery disease. *Anesthesiology* 1979; **51**: 393–397.
56. Rydvall A, Häggmark S, Nyhman H, Reiz S. Effects of enflurane on coronary haemodynamics in patients with ischaemic heart disease. *Acta Anaesthesiologica Scandinavica* 1984; **28**: 690–695.
57. Schaper W, Flameng W, Winkler B, Wusten B, Turschmann W, Neugebauer G, Carl M. Quantification of collateral resistance in acute and chronic experimental coronary occlusion in the dog. *Circulation Research* 1976; 39, 371–377.
58. Schulte-Sasse U, Hess W, Tarnow J. Haemodynamic responses to induction of anaesthesia using midazolam in cardiac surgical patients. *British Journal of Anaesthesia* 1982; **54**: 1053–1058.
59. Sill JC, Bove AA, Nugent M, Blaise GA, Dewey JD, Grabau C. Effects of isoflurane on coronary arteries and coronary arterioles in the intact dog. *Anesthesiology* 1987; **66**: 273–279.
60. Slogoff S, Keats AS. Does perioperative myocardial ischemia lead to postoperative myocardial infarction? *Anesthesiology* 1985; **62**: 107–114.
61. Slogoff S, Keats AS. Further observations on perioperative myocardial ischemia. *Anesthesiology* 1986; **65**: 539–542.
62. Sonntag H, Hellberg K, Schenk H-D, Donath W, Regensburger D, Kettler D, Duchanova H, Larsen R. Effects of thiopental (Trapanal) on coronary blood flow and myocardial metabolism in man. *Acta Anaesthesiologica Scandinavica* 1975; **19**: 69–78.
63. Sonntag H, Larsen R, Hilfiker O, Kettler D, Brockschnieder B. Myocardial blood flow and oxygen consumption during high-dose fentanyl anesthesia in patients

with coronary artery disease. *Anesthesiology* 1982; **56**: 417–422.

64. Sonntag H, Merin RG, Dontah U, Radke J, Schenk HD. Myocardial metabolism and oxygenation in man awake and during halothane anesthesia. *Anesthesiology* 1979; **51**: 204–210.
65. Stephan H, Sonntag H, Schenk HD, Kettler D, Khambatta HJ. Effects of propofol on cardiovascular dynamics, myocardial blood flow and myocardial metabolism in patients with coronary artery disease. *British Journal of Anaesthesia* 1986; **58**: 969–975.
66. Sybert PE, Hickey RF, Hoar PF, Verrier ED, Bainton CR. Effects of volatile anesthetics on the regulation of coronary blood flow. *Anesthesiology* 1983; **59**: A24.
67. Tarnow J, Eberlein HJ, Oser G, Patschke D, Schneider E, Schweichel E, Wilde J. Haemodynamik, Myokardkontraktilität, Ventrikelvolumina und Sauerstoffversorgung des Herzens unter verschiedenen Inhalationsanaesthetika. *Anaesthesist* 1977; **26**: 220–230.
68. Tarnow J, Markschies-Hornung A, Schulte-Sasse U. Isoflurane improves the tolerance to pacing-induced myocardial ischemia. *Anesthesiology* 1985; **64**: 147–156.
69. Waltier DC, Gross GJ, Brooks HL. Coronary-steal induced increase in myocardial infarct size after pharmacologic coronary vasodilation. *American Journal of Cardiology* 1980; **46**: 83–89.
70. Wilkinson PL, Hamilton WK, Moyers JR, Graham BG, Ports TA, Ullyot DJ, Chatterjee K. Halothane and morphine–nitrous oxide anaesthesia in patients undergoing coronary artery bypass operation. Patterns of intraoperative ischemia. *Journal of Thoracic and Cardiovascular Surgery* 1981; **82**: 372–382.
71. Wilkowski DAW, Sill JC, Bonta W, Owen R, Bove AA. Nitrous oxide constricts epicardial coronary arteries without effect on coronary arterioles. *Anesthesiology* 1987; **66**: 659–665.

Br. J. Anaesth. (1988), **61**, 85–96

ANAESTHETIC CONSIDERATIONS FOR THE PATIENT WITH CORONARY ARTERY DISEASE

C. PRYS-ROBERTS

The patient with coronary artery (ischaemic heart) disease may present to the anaesthetist in one of three ways. Those whose coronary arterial occlusion has reached the point at which tissue blood flow is compromised either at rest, in response to anxiety or emotion, or during exercise, present with symptoms of acute ischaemia (angina pectoris). Those who have already suffered one or more episodes of myocardial infarction give a history which identifies them as being at risk [61]. However, given the prevalence of coronary artery disease in most Western populations, the majority of patients with significant coronary disease present for anaesthesia and surgery, but give neither a history nor symptoms which identify them. Symptoms of angina occur during exercise when the cross-sectional area of a major coronary artery is reduced to 30% of normal, whereas angina at rest occurs only when the cross-sectional area is reduced to approximately 10% of normal. Patients whose coronary arteries are occluded to the extent that cross-sectional area is reduced by 50% may exhibit their first manifestations of myocardial ischaemia during induction of anaesthesia, tracheal intubation, or in response to surgical stimuli.

Coronary artery disease may occur in isolation, or in combination with the pathological process of vascular ageing, arteriosclerosis. The two conditions have differing impacts on the haemodynamic changes in response to anaesthesia and surgery. Hypertension is not a feature of coronary artery disease, and *vice-versa*, but where the two conditions co-exist, hypertension aggravates and accelerates the pathological processes of coronary artery disease. Patients older than 40 yr presenting for anaesthesia and surgery must therefore be considered at risk of any combination of these three conditions. Anaesthetic techniques must also be chosen to minimize haemodynamic changes which in the normal healthy patient cause no serious morbidity, but which, in the patient with coronary artery disease, can lead to serious morbidity or death.

Do risk factors influence the choice of anaesthesia?

Risk factors are a means of quantifying the probability that a number of pre-existing conditions may, singly or in combination, modify the outcome of anaesthesia and surgery [14, 15, 45, 55, 58, 61]. Let us take a simple example, that 10% of patients with a history of myocardial infarction will die if subjected to anaesthesia and surgery within 3 months of the infarct. Another way of looking at this statistic is that 90% of such patients *will not die*, however well or badly they are anaesthetized. Unless we can identify the factors which determine those patients who form the 10% who will die, the information is of no value as a prognostic index, or in making a choice of anaesthetic technique.

Can we identify potentially harmful physiological changes?

An alternative approach to the anaesthetic management of the patient with coronary artery disease is to identify those specific factors which precipitate an imbalance between coronary blood flow and myocardial oxygen requirements, and to choose anaesthetic drugs and techniques which avoid any physiological trespass. Previous articles in this issue have identified and expanded in detail on a number of these, and it is sufficient here to outline their relevance in clinical practice.

As coronary artery disease results in regional rather than global ischaemic changes, it is important to recognize those factors which result in redistribution of coronary blood flow, as much as those causing either a global decrease of coronary blood flow or an increase of myocardial oxygen

---

C. PRYS-ROBERTS, M.A., D.M., PH.D., F.F.A.R.C.S., F.F.A.R.A.C.S., Sir Humphry Davy Department of Anaesthesia, University of Bristol, Bristol Royal Infirmary, Bristol BS2 8HW.

uptake. In this respect the most important distinction is that between transmural ischaemia and subendocardial ischaemia.

Transmural ischaemia usually results from occlusion of, or spasm in, a major epicardial coronary artery, or a combination of both. It is recognized by the occurrence of electrocardiographic ST-segment elevation which commonly precedes myocardial infarction. Such changes are very infrequent during or shortly after anaesthesia, but are observed commonly in the casualty department or medical wards. Prinzmetal's variant angina, associated with coronary arterial spasm, also causes ST-segment elevation. It is also a rare event in association with anaesthesia and surgery.

Subendocardial ischaemia results from inadequate distribution of coronary blood flow to the inner layer of the myocardium [20], and is characterized by depression of the ST-segment. It is a common finding before, during and after surgery, and its severity and duration may be factors in the development of subendocardial infarction [24, 58]. Subendocardial ischaemia may be precipitated by factors which cause an increase of myocardial oxygen requirements beyond the range which can be supplied, either locally or globally, by the maximum available coronary blood flow. Characteristically, this is the result of hypertension, tachycardia, or both, tachycardia being the major determinant because of its effect in shortening the diastolic interval available for coronary blood flow. Hypertension may result also in an increase of left (and right) ventricular diastolic pressures which enhance the haemodynamic vice [20] limiting collateral perfusion in the subendocardium (fig. 1) [39]. Such is the probable course of events when myocardial ischaemia occurs following aortic cross-clamping [2, 26], where the sudden increase in the impedance to left ventricular (LV) ejection results in a marked increase in LV end-diastolic pressure in those patients whose coronary artery disease is sufficiently severe that the left ventricular muscle can neither maintain its force generation in the face of the increased load, nor relax adequately during early diastole.

Subendocardial ischaemia can be precipitated also when coronary blood flow is inadequate to meet the demand of the myocardium, which is usually reduced below normal during anaesthesia. Hypotension alone can precipitate ischaemia by decreasing the coronary diastolic perfusion pressure, but the ischaemia is often more severe when hypotension is combined with tachycardia [6].

PRINCIPLES OF ANAESTHESIA

It is clear from the preceding discussion, and the previous papers in this symposium, that the main

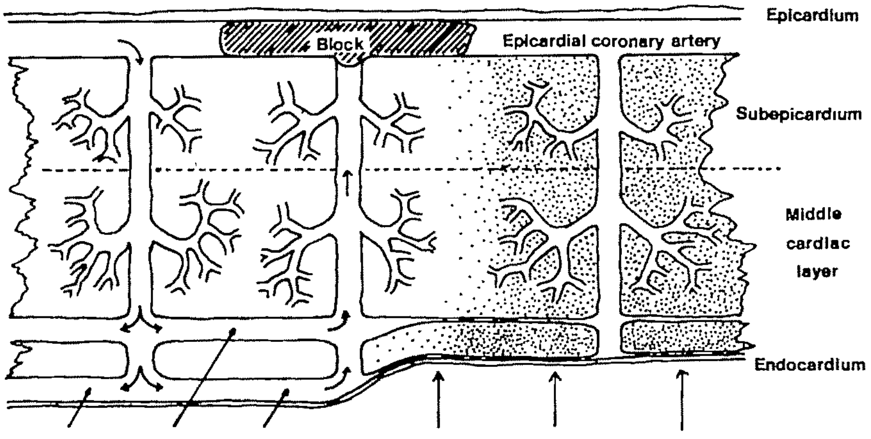

Epicardium
Block
Epicardial coronary artery
Subepicardium
Middle cardiac layer
Endocardium
Subendocardial collaterals
Ventricular intracavitary pressure

FIG. 1. Diagrammatic representation of a cross-section of the left ventricular myocardium in a patient with subendocardial ischaemia. The inner layer of the myocardium is supplied by penetrating branches of the epicardial coronary arteries. In a zone beyond a blockage in an epicardial area, the middle cardiac zone is perfused by the development of subendocardial collateral vessels. These vessels are in a state of chronic dilatation, and are normally patent during diastole, except when left ventricular diastolic pressure is increased, causing the "haemodynamic vice". (From [39], by courtesy of the publishers.)

principle in providing safe anaesthesia for the patient with coronary artery disease is to avoid those conditions which precipitate myocardial ischaemia, specifically to avoid tachycardia, with or without hypertension or hypotension.

The changes of arterial pressure and heart rate which occur during and after anaesthesia reflect a balance betwen the direct haemodynamic effects of anaesthetic agents and other drugs, the reflex haemodynamic responses to such changes of arterial pressure, the reflex haemodynamic responses to the noxious stimuli associated with surgery, and the degree to which the last of these are suppressed by the anaesthetic methods used.

How important are the haemodynamic responses to noxious stimulation in the generation of myocardial ischaemia? Let us consider the way in which humans respond to noxious stimulation [40]. A noxious stimulus is one which can cause potential or actual damage to cells, and may be produced by mechanical (surgical), chemical, thermal or radiation injury. Surgery sets up a continuous noxious stimulation, of varying degree and character, during and for a variable period after an operation. In addition to evoking the perception of pain (in a conscious subject), noxious stimulation also evokes a number of somatic and autonomic reflexes which Sherrington termed "pseudaffective" reflexes. These reflexes occur simultaneously with the perception of unpleasant sensory experiences [21,56], and are prominent particularly when evoked by stimulation of abdominal or thoracic viscera [8]. The continuation of noxious stimulation into the postoperative period also evokes a metabolic and endocrine response [22].

Autonomic responses

Noxious stimuli cause reflex activation of the sympathetic nervous system, which can be considered a part of the "Abwehrverhalten" (General Defence Reaction) as observed in animals by Hess and Brugger [17,19]. During clinical anaesthesia the manifestations of these responses may be modified by the use of drugs which specifically block central or peripheral transmission of sympathetic nervous action potentials (e.g. clonidine or β-adrenoceptor antagonists). The autonomic responses may be classified simply into sudomotor (sweating), haemodynamic and hormonal.

Haemodynamic responses represent the effects of increased sympatho–adrenal activity on the cardiovascular system. The most obvious effects are increased arterial pressure and heart rate, the two variables monitored most commonly in routine anaesthesia. These responses occur commonly in response to both anaesthetic (laryngoscopy) and surgical stimuli, even when anaesthetic concentrations are high enough to suppress sensory, motor and breathing responses. It is these haemodynamic responses which most commonly precipitate episodes of myocardial ischaemia during anaesthesia.

Noxious stimuli from the somatic distribution are important as a means of evoking reflex movements, but produce minimal autonomic disturbance. In contrast, noxious stimuli from the visceral distribution evoke stronger autonomic responses, particularly haemodynamic changes.

CHOICE OF ANAESTHESIA

Preoperative treatment

There is little doubt nowadays that pre-existing anti-anginal, anti-hypertensive, or anti-arrhythmic therapies should be continued up to and including the day of projected surgery. The dangers of abrupt withdrawal of β-adrenoceptor antagonists have been documented [27,34], and the advantages of maintained therapy in patients with hypertension or coronary artery disease, or both, have been emphasized repeatedly [41,42]. More recently, however, the advantages and problems relating to pre-existing therapy with calcium channel blockers have been highlighted [51]. While therapy with these drugs should also be maintained up to and including the day of surgery, it is also clear that the calcium channel blockers are not particularly effective, especially in everyday therapeutic doses, in suppressing sympathoadrenal responses to noxious stimuli during anaesthesia and surgery [16]. Consideration should be given to the option of supplementing such therapy with a low dose of a β-adrenoceptor antagonist (e.g. atenolol 50 mg) given by mouth on the morning of surgery. Patients who take nitrate therapy regularly for angina should be maintained on their current therapy, and should be given transdermal nitroglycerin paste applications [63].

Opinions differ concerning premedication of patients with coronary artery disease. Moffitt recommended heavy premedication with a combination of opioids and benzodiazepines given the night before and on the morning of surgery [31], while others maintain that oral administration of a benzodiazepine alone is adequate in patients whose other anti-anginal drug therapy is adequately maintained.

Induction of anaesthesia

Rapid injection of most i.v. induction agents, in a dose sufficient to induce anaesthesia and abolish the eyelash reflex, usually causes a decrease of both systolic and diastolic arterial pressure, the extent of the decrease being dependent on the agent used, the dose and the rate of injection. Of the commonly used induction agents, only ketamine provides an exception to this rule [50]; injection of between 0.5 and 1.5 mg kg^{-1} is associated with an increase of arterial pressures by up to 40% of the preinduction value.

The decrease of arterial pressure associated with thiopentone, methohexitone and midazolam (and to a lesser extent with etomidate) is commonly accompanied by a substantial (+3 to +50%) increase of heart rate. This is often and mistakenly attributed to a baroreflex response to the decrease of arterial pressure, but it is probable that the increase of heart rate which accompanies induction of anaesthesia is predominantly caused by a central release of vagotonic control of the heart. Propofol differs considerably from the other induction agents in that blood concentrations sufficient to maintain anaesthesia (1.7–4.5 μg ml^{-1}) do not appear to depress the sensitivity of baroreflex control of heart rate in the same way as do other induction agents, but cause a resetting of the baroreflex mechanism to allow slower heart rates in conjunction with decreased arterial pressure [9]. This could be interpreted as reflecting a central vagotonic or depression of sympathetic activity, and could be considered advantageous for the patient with coronary artery disease, provided arterial hypotension is minimized [33,35]. Arterial hypotension during induction of anaesthesia may result from a decrease of cardiac output or of systemic vascular resistance, or both. The degree to which each variable is affected depends on a number of factors, the most important of which is the relationship between the increase in heart rate (which tends to increase cardiac output) and the degree of venous dilatation. The latter results in a rapid redistribution of the blood volume from the intrathoracic compartment to the subdiaphragmatic compartment, thus decreasing both right and left ventricular filling [1].

A new approach to minimizing the decrease of arterial pressure during induction of anaesthesia is to use a computer-controlled infusion designed to reach a minimum effective blood anaesthetic concentration within 5 min [62]. This approach avoids the overshoot of the blood concentration of the relevant induction agent which inevitably follows the injection of a single loading dose of the drug. From the computer model for the infusion of propofol, a simple scheme for manual control of an infusion pump was devised, and shown to be almost as effective in achieving a steady blood concentration without an initial overshoot [52]. The computer and manual control schemes have both been shown to minimize the acute decrease of arterial pressure which occurs at induction of anaesthesia.

The role of opioids in the induction of anaesthesia

The synthetic opioids of the fentanyl series (fentanyl, alfentanil, sufentanil) exert minimal depression of cardiac performance, and have all been used, either alone or in combination with low doses of other induction agents, to induce anaesthesia in patients with coronary artery disease. The concept of opioid induction of anaesthesia was a logical sequel to neurolept-analgesic techniques, and has become popular particularly for induction of anaesthesia in cardiac surgery [5]. Subsequent studies have shown the value of moderate doses (fentanyl 8–10 μg kg^{-1}; alfentanil 50–100 μg kg^{-1}; sufentanil 1 μg kg^{-1}) as a prelude to the induction of anaesthesia with minimal doses of thiopentone, etomidate, methohexitone or propofol. The addition of nitrous oxide to any of these opioids may cause profound impairment of myocardial performance [37] in animals, and decreased arterial pressure and cardiac output (fig. 2) in man [42].

Alfentanil has a specific advantage over the other drugs for patients undergoing surgery of relatively short duration, in that its low initial volume of distribution allows the appropriate plasma concentration to be achieved at relatively low loading doses (20–50 μg kg^{-1}), and its elimination half-time is significantly shorter than that of other opioids.

Sufentanil was introduced into clinical practice in the mid '70s and has achieved a certain popularity in anaesthesia for coronary artery surgery [5]. In combination with nitrous oxide,

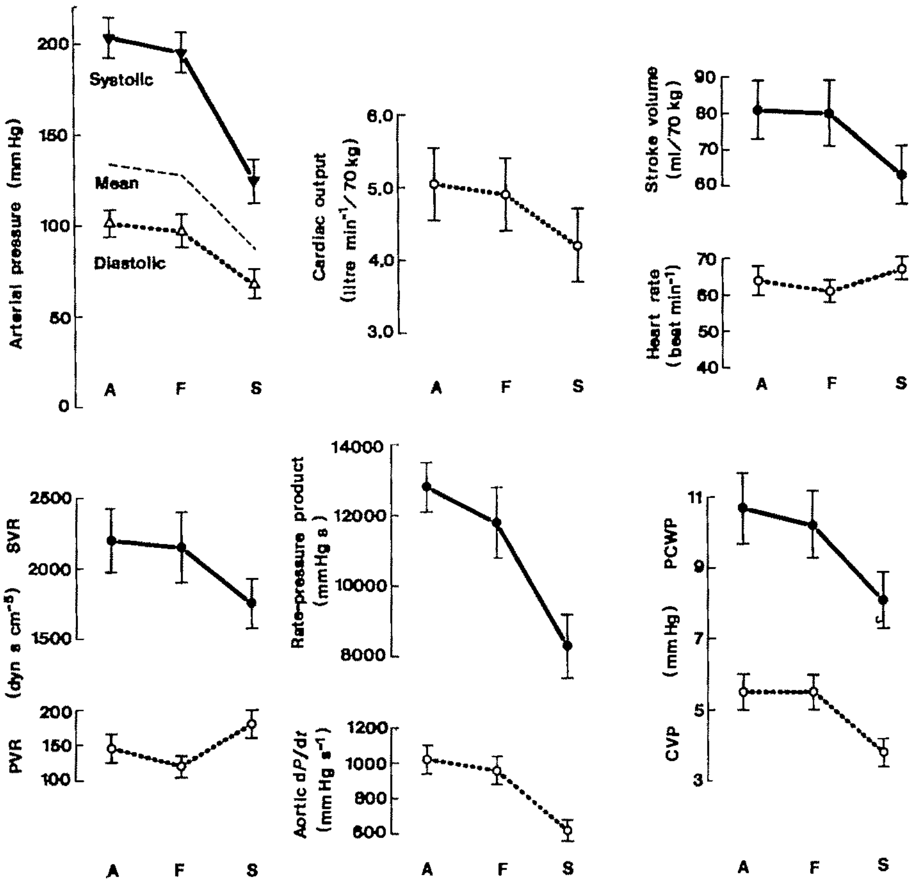


FIG. 2. Haemodynamic responses awake (A) and after induction of anaesthesia with fentanyl 8 μg kg^{-1} (F) followed by administration of 67% nitrous oxide (S) in 13 hypertensive patients, many with coincident coronary artery disease, receiving high doses of β-adrenoceptor antagonists. Note the profound decrease of arterial pressures, cardiac output and stroke volume following ventilation of the lungs with nitrous oxide. (From [42], by courtesy of the author and the Editor of *Acta Anaesthesiologica Scandinavica*.)

sufentanil appears to produce greater cardiovascular stability than other opioids [64], and as its pharmacokinetic profile is similar to that of fentanyl, it may prove to be a highly suitable opioid for patients with coronary artery disease. Its shorter terminal half-life makes it a more suitable opioid than fentanyl for the patient undergoing short-term surgery.

Volatile anaesthetics

Moffitt and his colleagues performed a series of studies of induction and maintenance of anaesthesia in patients with coronary artery disease with preserved left ventricular function; these studies were reviewed comprehensively by Moffitt and Sethna [31]. Induction of anaesthesia with a volatile anaesthetic may not be considered the most appropriate method in adult patients, and Moffitt's data suggest that enflurane or isoflurane administered in oxygen causes a greater decrease of arterial pressure and a greater increase of heart rate than halothane or fentanyl, whereas all three volatile anaesthetics decreased myocardial blood flow to a greater extent (−32 to −50%) than fentanyl (−12%).

Laryngoscopy and tracheal intubation

Based on the magnitude of the arterial pressure and heart rate changes, and the increases in plasma catecholamine concentrations evoked by laryngoscopy and tracheal intubation, these must be considered to be the most potent noxious

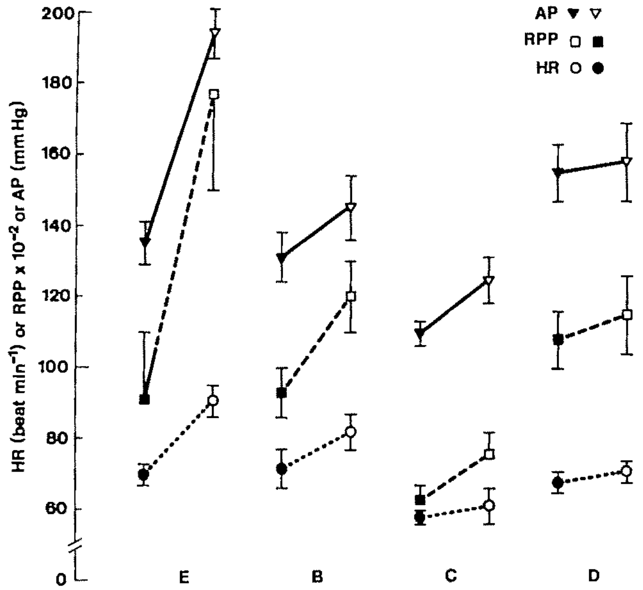


FIG. 3. Responses of systolic arterial pressure, heart rate and rate–pressure product to laryngoscopy and tracheal intubation in four groups of hypertensive patients. Group E represents a group of 14 hypertensive patients treated with agents other than β-adrenoceptor antagonists, of whom 41% developed ECG evidence of subendocardial ischaemia in response to the stimulus. Group B consists of 10 patients with moderate to severe hypertension who were given practolol 100 mg every 8 h for 48 h before anaesthesia. Group C are 21 patients (13 hypertensive, eight with coronary artery disease) under stable therapy with β-adrenoceptor antagonists, who were maintained on therapy up to and including the day of surgery. Group D were 13 severely hypertensive patients from [42]. (From [43], by courtesy of Astra Pharmaceuticals.)

stimuli in respect of their effects on autonomic nervous activity. Distension of balloons (to simulate stretching of tissues) in the nasal passages, pharynx or larynx, evoke powerful reflex activity in efferent cervical sympathetic nerves [64]. I.v. and inhalation anaesthetics suppress these responses to greater or lesser degree, thus the arterial pressure (and heart rate) at the peak of the haemodynamic response to laryngoscopy represents a balance between the direct hypotensive effects of the anaesthetic, and the efficacy with which the latter suppresses the response to the noxious stimulus.

The volatile anaesthetics (halothane, enflurane, isoflurane) were found to be less effective in blocking the heart rate and pressor responses to laryngoscopy and intubation than was fentanyl [31].

Induction of anaesthesia with opioids, as described above, with or without i.v. anaesthetics, can be very effective in suppressing the haemodynamic response to laryngoscopy and intubation, although there are no studies which specifically compare the effects of fentanyl, alfentanil and sufentanil in this respect. Infusion of nitroglycerin 0.9 μg kg^{-1} min^{-1} to supplement fentanyl 3 μg kg^{-1} produced greater stability of pulmonary capillary wedge pressures and a significant reduction in the incidence of myocardial ischaemia (5% against 20%) compared with fentanyl 8 μg kg^{-1}, during laryngoscopy and intubation in patients with stable angina [13].

The responses can be modified also by beta-adrenoceptor antagonists, administered either by mouth before anaesthesia, or i.v. at the induction of anaesthesia (fig. 3). Moderate doses of opioids for induction of anaesthesia combined with pre-existing β-adrenoceptor antagonist therapy have been found to be totally effective in patients with hypertension and coronary artery disease [42].

Maintenance of anaesthesia

The choice of anaesthetic technique and agents is dependent largely on the nature of the proposed surgery and the extent to which the surgical stimulus can be predicted to induce autonomic responses. For the patient with coronary artery disease the main objective is to avoid tachycardia, with or without arterial hypotension or hypertension. These requirements dictate the combinations of drugs which are appropriate in any specific circumstance. The reader is recommended to consult the review by Moffitt and Sethna [31] for a comprehensive comparison of the effects of halothane, enflurane or isoflurane with those of morphine or fentanyl for maintenance of anaesthesia in patients with coronary disease.

Three options are available: regional anaesthesia (with or without appropriate sedation), general anaesthesia, or a combination of both. For many years purists have advocated one of the two former options, arguing that the combination of general and regional anaesthesia may cause greater cardiovascular instability than either technique alone. These concerns apply specifically to the combination of general anaesthesia with either spinal or extradural anaesthesia for abdominal or thoraco-abdominal surgery, in that the potential for arterial hypotension is greater if the sympathetic nerve supply to the pelvis and lower limbs is blocked simultaneously with that of the splanchnic area. While this may be true of a "high" spinal extending from T6–8 down to the sacral region, or a lumbar extradural block covering the same segmental distribution, it is not true necessarily for segmental blockade limited to the splanchnic distribution alone (e.g. T6–T12). Experience in patients with hypertension or coronary artery disease has shown that arterial pressures may certainly be lower with combined general and regional anaesthesia than with regional anaesthesia alone [10,49], although the absolute arterial pressure can be controlled by the judicious use of volume expansion, with or without simultaneous infusion of vasopressors [36]. Provided the segmental blockade is limited to cover only those segments in which the noxious stimuli are induced, regional blockade has the advantage of suppressing the autonomic response to intra-abdominal manipulation, and providing a means of postoperative pain relief.

Volatile anaesthetics and coronary artery disease

Volatile anaesthetics exert a dose-dependent decrease of arterial pressure in normal patients and those with coronary artery disease. The degree of arterial hypotension varies from agent to agent, but tends to be greater in the older patient. When considering the choice of volatile agent in the patient with coronary disease, it is necessary to balance the direct haemodynamic effect of the anaesthetic in the absence of surgery, and the extent to which the specific anaesthetic suppresses the haemodynamic responses to noxious stimulation. These relationships are by no means as simple as may appear at first, in that patients with coronary artery disease may be taking β-adrenoceptor antagonists or calcium channel blockers, or both, and these may considerably modify the haemodynamic effects of the anaesthetic. The β-adrenoceptor antagonists are effective also in blocking some of the haemodynamic responses to sympathetic nervous activation, whereas the calcium channel blockers are relatively ineffective [16].

Trichloroethylene may appear to many to be an outmoded and irrelevant anaesthetic, particularly in the context of coronary artery disease. Nevertheless, at least one major cardiac centre in the United Kingdom regularly uses trichloroethylene during cardiac surgery, partly for the benefit of the prolonged analgesia associated with its slow elimination from the body, but also because it appears to cause little direct impairment of cardiac function. While there are few studies which give a comprehensive view of the haemodynamic effects of trichloroethylene in man, studies in the dog [53] permit comparisons with halothane, with and without β-adrenoceptor antagonists. Trichloroethylene anaesthesia is associated with an increase of heart rate in the dog, which appears to offset any effects of the drug on arterial pressure, certainly up to inspired concentrations of 0.8%. Following propranolol 20 mg kg^{-1} day^{-1} arterial pressure and cardiac output decrease in response to increasing concentrations of trichloroethylene, in the absence of a compensatory tachycardia. If this is a potential relative benefit in the patient with coronary artery disease is difficult to assess in the absence of appropriate studies.

Halothane, in low concentrations (< 1.0% alveolar) administered alone or with nitrous oxide, has been studied extensively in patients with coronary artery disease. By decreasing arterial pressure and cardiac output, halothane decreases myocardial work to a greater extent than it decreases coronary blood flow [4,18,32,47], allowing the heart globally to extract less oxygen, minimizing the probability of myocardial ischaemia [59]. None of these studies found any evidence that halothane promoted myocardial lactate production (evidence of global or local ischaemia); indeed Moffitt and colleagues [32] found myocardial lactate extraction in all their patients.

Studies in experimental animals with critical coronary artery stenosis have shown that increasing concentrations of halothane may cause ischaemia and ventricular dyssynchrony by reducing coronary perfusion pressure [25]. Nitrous oxide, substituted for nitrogen in similar dogs anaesthetized with halothane, produced moderate depression of global myocardial function, and decreased regional shortening in the segment supplied by a critically stenosed coronary artery [44].

Enflurane also decreases arterial pressure and cardiac output, decreasing myocardial work and myocardial oxygen uptake to a greater extent than coronary blood flow [29]. Sternotomy and other surgical stimuli did not induce an increase of arterial pressure or myocardial work, unlike the other anaesthetics studied by Moffitt's group, and no increased lactate concentrations were found in either arterial or coronary sinus blood. Other studies found similar results, although higher concentrations of enflurane (1.4% end-tidal) caused a 50% decrease of arterial pressure, with evidence of myocardial ischaemia in four of 11 patients [54].

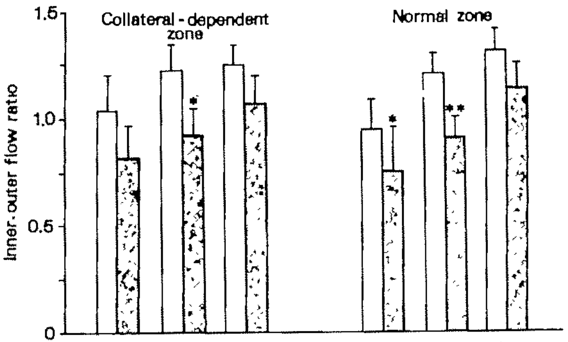


FIG. 4. Effect of isoflurane (shaded columns) on the distribution of coronary perfusion to the inner and outer cardiac layers in collateral dependent and normal zones of the dog heart (mean ± SEM, $n = 8$). Comparisons are made at three coronary flows. Isoflurane consistently decreased the inner: outer flow ratio at all flows. At the mid-flow level (80% of the autoregulated value) isoflurane (0.94% end-tidal) caused a significant increase of flow to the outer layers of the normal zone at the expense of decreased flow to the inner layers of the collateral-dependent zone. $^*P < 0.05$; $^{**}P < 0.02$. (From [7], by courtesy of the authors and the Editor of *Anesthesiology*.)

Isoflurane differs from halothane and enflurane in that the decrease in arterial pressure it causes in patients with coronary arterial disease is the result of decreased systemic vascular resistance, but with no change of cardiac output [28]. Isoflurane is a potent coronary arteriolar dilator and may cause a "steal phenomenon" (fig. 4) in patients with coronary arterial disease as a result of redistribution of coronary blood flow from potentially ischaemic areas to normally perfused areas [7,28,38,48,57]. For a detailed discussion of this topic the reader is referred to Reiz's review in this issue [46].

Isoflurane, especially at higher concentrations, may cause myocardial ischaemia to a greater extent than other volatile anaesthetics, and it may be prudent to avoid its use in circumstances where high concentrations may be necessary. This may be relevant particularly in patients with known subendocardial ischaemia, as the predilection of isoflurane for small arterioles rather than the larger epicardial arteries may result in redistribution of myocardial perfusion with resultant ischaemia.

The contribution of opioids may be considered under two headings: the use of opioids alone or with nitrous oxide, and their use to supplement volatile anaesthetics.

The popularity of opioids as the sole drug for cardiac anaesthesia stemmed from the introduction of morphine anaesthesia in the late '60s. Fentanyl and its analogues, sufentanil and alfentanil, have become popular for coronary revascularization surgery, mainly because these drugs cause minimal impairment of left ventricular function even in those patients with severe pre-existing dysfunction, decreased heart rate and reduced myocardial work [5,23,31,60]. However, the ability of these opioids to suppress the haemodynamic response to noxious stimulation is controversial [31]. Ausems and his colleagues [3] concluded from their dose–response studies on alfentanil in man, that the various stimuli which occur during the operative period require different concentrations of alfentanil for suppression. They found that the highest concentrations (475 ± 28 ng ml^{-1}) were required to suppress the haemodynamic response to laryngoscopy and intubation, and that approximately half that concentration suppressed the response to skin incision. They also found that the plasma concentrations required during upper abdominal surgery (412 ± 135 ng ml^{-1}) were much higher than those required for lower abdominal or breast surgery. The high infusion rates required to achieve these blood concentrations, and the possible delay in achieving adequate postoperative spontaneous ventilation suggest that the combination of lower doses of opioids with volatile anaesthetics (see below) would be more appropriate in the patient with coronary disease.

Based on their numerous studies, Moffitt and Sethna [31] concluded that a combination of opioids with a volatile anaesthetic, without nitrous oxide, would provide the best conditions for surgery in patients with coronary artery disease. This view is based on their studies with halothane or enflurane [30] as supplements to anaesthesia induced and maintained with "moderate" doses (30 μg kg^{-1}) of fentanyl, in which they found minimal depression of myocardial function during the period of anaesthesia before the onset of surgery, and adequate suppression of the haemodynamic response to noxious stimulation during surgery. As all the patients in the series studied by Moffitt and his colleagues had well preserved ventricular function, one cannot extrapolate their findings to the patient with ventricular dyssynchrony, or with left ventricular failure.

Regional blockade, with or without general anaesthesia

Spinal or extradural blockade can be very effective in suppressing the haemodynamic responses to noxious surgical stimuli, especially those arising from the viscera. However, unless the extent of segmental sympathetic denervation is controlled carefully, the ensuing arterial hypotension may be more dangerous than the hyperdynamic response to noxious stimulation.

Segmental thoracic extradural blockade has the advantage that the volume of local anaesthetic required to block the visceral segments (T5–9) can be limited to spare the sympathetic innervation of the legs, minimizing the degree of venodilatation and arterial hypotension. Thoracic extradural blockade, with or without general anaesthesia was tolerated well by hypertensive patients, many of whom had coincident coronary artery disease, and were treated with β-adrenoceptor antagonists [10]. It has the further advantage of providing continuous pain relief and blockade of the responses to noxious stimulation in the postoperative period.

Thoracic extradural blockade has been shown also to reduce myocardial infarct size after deliberate coronary artery occlusion in dogs [11].

CONCLUSIONS

The general principles of anaesthetic management for the patient with coronary artery disease may be summarized in a few simple rules which encourage the achievement of a balance between myocardial oxygen demand and supply, and the prevention or avoidance of those factors which might disturb such a balance. The general aim is to maintain the circulation in a slightly hypodynamic state without prejudicing ventricular function [31].

Effective preoperative drug therapy with calcium channel blockers, β-adrenoceptor antagonists, nitrates and angiotensin-converting enzyme inhibitors should be maintained up to, and including, the day of surgery. Increased oral doses of β-adrenoceptor antagonists should be considered in patients receiving low doses of these drugs or none at all. Clonidine has been shown to reduce opioid requirement during anaesthesia for coronary artery bypass surgery, while improving haemodynamic stability and the release of catecholamines [12].

Premedication should be adequate to sedate the patient sufficiently to prevent the haemodynamic consequences of apprehension, but there is considerable controversy regarding the requirement for heavy sedation as proposed by Moffitt [31].

The use of moderate doses of the potent opioids related to fentanyl enables induction of anaesthesia to be achieved without an increase of heart rate, while minimizing doses of i.v. anaesthetics and contributing to the suppression of the haemodynamic responses to the subsequent laryngoscopy and intubation.

The choice of volatile anaesthetic to supplement the opioids for maintenance of anaesthesia is probably less critical than recent publications might suggest. While isoflurane may cause a redistribution of coronary blood flow away from ischaemic areas, there is little evidence that low concentrations of isoflurane are harmful to such patients. Nevertheless, enflurane combined with fentanyl appears to have advantages over other combinations. There is growing evidence that nitrous oxide can precipitate ischaemia when combined with either opioids or volatile anaesthetics in patients with severe coronary artery disease, especially those with compromised left ventricular function.

Nitrates and calcium channel blockers should be used as coronary vasodilators, and to reduce myocardial work when other anaesthetic measures have failed. By contrast, positive inotropic agents such as dopamine or dobutamine should be used to maintain ventricular performance. β-Adrenoceptor antagonists may be necessary to control heart rate. Implicit in the use of these various therapeutic measures is the need to use extensive haemodynamic monitoring in order to allow close control of arterial pressure, heart rate and pulmonary arterial wedge pressures.

REFERENCES

1. Arndt JO. The low pressure system: the integrated function of veins. *European Journal of Anaesthesiology* 1986; 3, 343–370.
2. Attia RR, Murphy, JD, Snider M, Lappas, DG, Darling RC, Lowenstein, E. Myocardial ischemia due to infrarenal aortic cross-clamping during aortic surgery in patients with severe coronary artery disease. *Circulation* 1977; 53: 961–965.
3. Ausems ME, Hug CC jr, Stanski DR, Burm AGL. Plasma concentrations of alfentanil required to supplement nitrous oxide anesthesia for general surgery. *Anesthesiology* 1986; 65: 362–373.
4. Bastard OG, Carter JG, Moyers JR, Bross BA. Circulatory effects of isoflurane in patients with ischemic heart disease: a comparison with halothane. *Anesthesia and Analgesia* 1984; 63: 635–639.
5. Bovill JG, Sebel PS, Stanley TH. Opioid analgesics in anesthesia: with special reference to their use in cardiovascular anesthesia. *Anesthesiology* 1984; 61: 731–755.
6. Buffington CW. Impaired systolic thickening associated with halothane in the presence of a coronary stenosis is mediated by changes in hemodynamics. *Anesthesiology* 1986; 64: 632–640.
7. Buffington CW, Romson JL, Levine A, Duttlinger NC, Huang AH. Isoflurane induces coronary steal in a canine model of chronic coronary occlusion. *Anesthesiology* 1987; 66: 280–292.
8. Cervero F. Visceral nociception: peripheral and central aspects of visceral nociceptive systems. *Philosophical Transactions of the Royal Society (London) B* 1985; 308: 325–335.
9. Cullen PM, Turtle M, Prys-Roberts C, Way WL, Dye J. Effect of propofol anesthesia on baroreflex activity in humans. *Anesthesia and Analgesia* 1987; 66: 1115–1120.
10. Dagnino J, Prys-Roberts C. Studies of anaesthesia in relation to hypertension. VI: Cardiovascular responses to extradural blockade of treated and untreated hypertensive patients. *British Journal of Anaesthesia* 1984; 56: 1065–1073.
11. Davis RF, DeBoer WV, Maroko PR. Thoracic epidural anesthesia reduces myocardial infarct size after coronary artery surgery. *Anesthesia and Analgesia* 1986; 65: 711–717.
12. Flacke JW, Bloor BC, Flacke WE, Wong D, Dazza S, Stead SW, Laks H. Reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary bypass surgery. *Anesthesiology* 1987; 67: 11–19.
13. Fusciardi J, Godet G, Bernard JM, Bertrand M, Kieffer E, Viars P. Roles of fentanyl and nitroglycerin in prevention of myocardial ischemia associated with laryngoscopy and tracheal intubation in patients undergoing operations of short duration. *Anesthesia and Analgesia* 1986; 65: 617–624.
14. Goldman L. Assessment of the patient with known or suspected heart disease for non-cardiac surgery. *British Journal of Anaesthesia* 1988; 61: 38–43.
15. Goldman L, Caldera DL, Nussbaum SR, Southwick FS, Krogstad D, Murray B, Burke DS, O'Malley TA, Goroll AH, Caplan CH, Nolan J, Carabello B, Slater EE. Multifactorial index of cardiac risk in noncardiac surgical procedures. *New England Journal of Medicine* 1977; 297: 845–850.
16. Gorven AM, Cooper GM, Prys-Roberts C. Haemodynamic disturbances during anaesthesia in a patient receiving calcium channel blockers. *British Journal of Anaesthesia* 1986; 58: 357–360.
17. Hess WR, Brugger M. Das subcorticale Zentrum der affektiven Abwehrreaktion. *Helvetica Physiologica Acta* 1943; 1: 35–70.
18. Hilfiker O, Larsen R, Sonntag H. Myocardial blood flow and oxygen consumption during halothane–nitrous oxide anaesthesia for coronary revascularization. *British Journal of Anaesthesia* 1983; 55: 927–932.
19. Hilton SM. The defence-arousal system and its relevance for circulatory and respiratory control. *Journal of Experimental Biology* 1982; 100: 159–181.
20. Holsinger JW jr, Eliot RS. The potential role of the subendocardium in the pathogenesis of myocardial infarction. *Heart and Lung* 1972; 1, 356–361.
21. Jänig W. Systemic and specific autonomic reactions in pain: efferent, afferent and endocrine components. *European Journal of Anaesthesiology* 1985; 2: 319–346.
22. Kehlet H. The modifying effect of general and regional anesthesia on the endocrine-metabolic response to surgery. *Regional Anesthesia* 1982; 7 (Suppl.): S38–S48.
23. Larsen R, Sonntag H, Schenk HD, Radke J, Hilfiker O. Die Wirkung von Sufentanil und Fentanyl auf Hämodynamik, Koronardurchblutung und myocardialen Metabolismus des Menschen. *Anaesthesist* 1980; 29: 277–279.
24. Levine HD. Subendocardial infarction in retrospect: pathologic, cardiographic, and ancillary features. *Circulation* 1985; 72: 790–800.
25. Lowenstein E, Foëx P, Francis CM, Davies WL, Yusuf S, Ryder WA. Regional ischemic dysfunction in myocardium supplied by a narrowed coronary artery with increasing halothane concentration in the dog. *Anesthesiology* 1981; 55: 349–359.
26. Meloche R, Pottecher T, Audet J, Dufresne O, LePage C. Haemodynamic changes due to clamping of the abdominal aorta. *Canadian Anaesthetists Society Journal* 1977; 24: 20–34.
27. Miller RR, Olson HG, Amsterdam EA, Mason DT.

Propranolol withdrawal rebound phenomenon. *New England Journal of Medicine* 1975; **293**: 416–418.

28. Moffitt EA, Barker RA, Glenn JJ, Imrie DD, DelCampo C, Landymore RW, Kinley CE, Murphy DA. Myocardial metabolism and hemodynamic responses with isoflurane anesthesia for coronary artery surgery. *Anesthesia and Analgesia* 1986; **65**: 53–61.
29. Moffit EA, Imrie DD, Scovil JE, Glenn JJ, Cousin CL, DelCampo C, Sullivan JA, Kinley CE. Myocardial metabolism and haemodynamic responses with enflurane anesthesia for coronary artery surgery. *Canadian Anaesthetists Society Journal* 1984; **31**: 604–610.
30. Moffitt EA, McIntyre AJ, Barker RA, Imrie DD, Murphy DA, Landymore RW, Kinley CE. Myocardial metabolism and hemodynamic responses with fentanyl–enflurane anesthesia for coronary arterial surgery. *Anesthesia and Analgesia* 1986; **65**: 46–52.
31. Moffitt EA, Sethna DH. The coronary circulation and myocardial oxygenation in coronary disease. Effects of anesthesia. *Anesthesia and Analgesia* 1986; **65**, 413–459.
32. Moffitt EA, Sethna DH, Bussell JA, Raymond MJ, Matloff JM, Gray RJ. Myocardial metabolism and hemodynamic responses to halothane or morphine anesthesia for coronary artery surgery. *Anesthesia and Analgesia* 1982; **61**: 979–985.
33. Monk CR, Coates DP, Prys-Roberts C, Turtle MJ, Spelina KR. Haemodynamic effects of prolonged propofol infusions supplementing nitrous oxide anaesthesia for peripheral vascular surgery. *British Journal of Anaesthesia* 1987; **59**: 954–960.
34. Nattel S, Rangno RE, VanLoon G. Mechanism of propranolol withdrawal phenomena. *Circulation* 1979; **59**: 1158–1164.
35. Patrick MR, Blair IJ, Feneck RO, Sebel PS. A comparison of the haemodynamic effect of propofol (Diprivan) and thiopentone in patients with coronary artery disease. *Postgraduate Medical Journal* 1985; **61** (Suppl. 3): 23–27.
36. Pereira E, Millard RK, Prys-Roberts C, Hutton P. Use of phenylephrine in the adaptive closed-loop control of arterial pressure. *British Journal of Anaesthesia* 1986; **58**: 816P.
37. Philbin DM, Foëx P, Drummond GA, Lowenstein E, Ryder WA, Jones LA. Post-systolic shortening of canine left ventricle supplied by stenotic coronary artery when nitrous oxide is added in the presence of narcotics. *Anesthesiology* 1985; **62**: 166–174.
38. Priebe H-J. Differential effects of isoflurane on regional right and left ventricular performances, and on coronary, systemic and pulmonary hemodynamics in the dog. *Anesthesiology* 1987; **66**: 262–272.
39. Prys-Roberts C. Hypertension and systemic arterial disease. In: Vickers MD, ed. *Medicine for Anaesthetists*, 3rd Edn. Oxford: Blackwell Scientific, 1988.
40. Prys-Roberts C. Editorial: Anaesthesia, a practical or impractical construct? *British Journal of Anaesthesia* 1987; **59**: 1341–1345.
41. Prys-Roberts C. Anaesthesia and hypertension. *British Journal of Anaesthesia* 1984; **56**: 711–724.
42. Prys-Roberts C. Interactions of anaesthesia and high pre-operative doses of β-receptor antagonists. *Acta Anaesthesiologica Scandinavica* 1982; (Suppl.) **76**: 47–53.
43. Prys-Roberts C. Cardiovascular responses to anaesthesia and surgery in patients receiving B-receptor antagonists. In: van Dijk B, van Elzakker AHM, Poppers P, eds. *B-blockade and Anaesthesia*. Gothenburg, Lindgren & Soner, 1980.
44. Ramsay JG, Arvieux CC, Foëx P, Philbin DM, Jeavons P, Ryder WA, Jones LA. Regional and global myocardial function in the dog when nitrous oxide is added to halothane in the presence of critical coronary artery constriction. *Anesthesia and Analgesia* 1986; **65**: 431–436.
45. Rao TLK, Jacobs KH, El-Etr AA. Reinfarction following anesthesia in patients with myocardial infarction. *Anesthesiology* 1983; **59**: 499–505.
46. Reiz S. Myocardial ischaemia associated with general anaesthesia. A review of clinical studies. *British Journal of Anaesthesia* 1988; **61**: 68–84.
47. Reiz S, Bålfors E, Gustavsson B, Haggmark S, Nath S, Rydvall A, Truedsson H. Effects of halothane on coronary haemodynamics and myocardial metabolism in patients with ischaemic heart disease and heart failure. *Acta Anaesthesiologica Scandinavica* 1982; **26**: 133–138.
48. Reiz Z, Bålfors E, Sorenson MB, Ariola S, Friedman A, Truedson H. Isoflurane—a powerful coronary vasodilator in patients with coronary artery disease. *Anesthesiology* 1983; **59**: 91–97.
49. Reiz S, Nath S, Rais O. Effects of thoracic epidural block and prenalterol on coronary vascular resistance and myocardial metabolism in patients with coronary artery disease. *Acta Anaesthesiologica Scandinavica* 1980; **24**: 11–16.
50. Reves JG, Kissin I. Pharmacology of anesthetic drugs: Intravenous Anesthetics. In: Kaplan JA, ed. *Cardiac Anesthesia Vol. 2 Cardiovascular Pharmacology*. New York, Grune & Stratton, 1983; 3–31.
51. Reves JG, Kissin I, Lell WA, Tosone S. Calcium entry blockers: Uses and implication for anesthesiologists. *Anesthesiology* 1982; **57**: 504–514.
52. Roberts FL, Dixon J, Lewis, GTR, Tackley RM, Prys-Roberts C. Induction and maintenance of propofol anaesthesia: a manual infusion scheme. *Anaesthesia* 1988; (Suppl.) **43**: 14–17.
53. Roberts JG, Foëx P, Clarke TNS, Bennett MJ, Saner CA. Haemodynamic interactions of high-dose propranolol and anaesthesia in the dog. III: The effects of haemorrhage during halothane and trichloroethylene anaesthesia. *British Journal of Anaesthesia* 1976; **48**: 411–418.
54. Rydvall A, Haggmark S, Nyhman H, Reiz S. Effects of enflurane on coronary haemodynamics in patients with ischaemic heart disease. *Acta Anaesthesiologica Scandinavica* 1984; **28**: 690–695.
55. Sapala JA, Ponka JL, Duvernoy WFC. Operative and nonoperative risks in the cardiac patient. *Journal of the American Geriatric Society* 1975; **23**: 529–534.
56. Schmidt RF (ed.) *Fundamentals of Sensory Physiology*, 3rd Edn. Berlin, Heidelberg, New York: Springer-Verlag, 1985.
57. Sill JC, Bove AA, Nugent M, Blaise GA, Dewey JD, Grabau C. Effects of isoflurane on coronary arteries and coronary arterioles in the intact dog. *Anesthesiology* 1987; **66**: 273–279.
58. Slogoff S, Keats AS. Does perioperative myocardial ischemia lead to postoperative myocardial infarction? *Anesthesiology* 1985; **61**: 107–114.
59. Smith G, Rogers K, Thorburn J. Halothane improves the balance of oxygen supply to demand in acute experimental myocardial ischaemia. *British Journal of Anaesthesa* 1980; **52**: 577–583.
60. Sonntag H, Larsen R, Hilfiker O, Kettler D, Brock-

schneider B. Myocardial blood flow and oxygen consumption during high-dose fentanyl anesthesia in patients with coronary disease. *Anesthesiology* 1982; **56**: 417–422.

61. Steen PA, Tinker JH, Tarhan S. Myocardial reinfarction after anesthesia and surgery. *Journal of the American Medical Association* 1978; **239**: 2566–2570.
62. Tackley RM, Lewis GTR, Prys-Roberts C, Boaden RW, Harvey JT. Open loop control of propofol infusions. *British Journal of Anaesthesia* 1987; **59**: 935P.
63. Taylor WR, Forrester JS, Magnusson P, Takano T, Chatterjee K, Swan HJC. Hemodynamic effects of nitroglycerin ointment in congestive heart failure. *American Journal of Cardiology* 1976; **38**: 469–473.
64. Tomori Z, Widdicombe JG. Muscular, bronchomotor and cardiovascular reflexes elicited by mechanical stimulation of the respiratory tract. *Journal of Physiology (London)* 1969; **200**: 25–49.

Br. J. Anaesth. (1988), 61, 97–104

ANAESTHESIA FOR CORONARY ARTERY BYPASS GRAFT

J. B. STREISAND AND K. C. WONG

Coronary artery disease (CAD) continues to be a major health problem in the United States. There are an estimated 10000000 patients afflicted with this disease leading to 150000 coronary artery bypass grafts (CABG) performed annually. While several factors (including a better understanding of CAD, refined surgical technique, technological and pharmacological improvements in cardiopulmonary bypass and myocardial preservation, and newer and improved anaesthetic agents) have contributed to the recent decrease in morbidity and mortality from CABG, the role of the anaesthetist cannot be understated. Slogoff and Keats demonstrated an 11-fold difference in postoperative myocardial infarction (MI) rate among CABG patients managed by nine different anaesthetists [35]. A strong correlation between intraoperative tachycardia and myocardial ischaemia leading to postoperative morbidity (MI) was found. This study confirmed the previous observations that haemodynamic stability is of paramount importance in the anaesthetic management of CABG surgery.

The anaesthetist who renders care to the CABG patient must be totally familiar with the patient's preoperative condition, with respect to both cardiac and non-cardiac medical problems. Also, he must be knowledgeable of, and capable of using, the various new monitoring techniques and new anaesthetic agents, to formulate an anaesthetic plan that is appropriate for each individual patient. While technical control of cardiopulmonary bypass (CPB) is relegated usually to the surgeon and pump technician, the physiological response to CPB must be familiar to the cardiac anaesthetist. Finally, the probability of a smooth recovery can be improved by understanding the principles of mechanical ventilation and the potential complications seen during the immediate postoperative period in this patient population.

This brief review of the anaesthetic principles for CABG surgery encompasses selected topics and controversial issues seen during the perioperative period.

Preoperative evaluation

The anaesthetist should be totally familiar with the patient's preoperative status. This information is important not only in planning anaesthetic management, but also in evaluating risk and predicting outcome. Preoperative factors that have been shown to affect outcome adversely include left main coronary disease, congestive heart failure, myocardial dyskinesia, age, female sex, ejection fraction, left ventricular end-diastolic pressure (LVEDP) and the priority of the operation (elective *v.* emergency) [17]. While many of these predictive factors cannot be altered, optimizing the patient's condition with respect to the above factors before surgery should improve outcome.

The presence or absence of congestive heart failure with limited cardiac reserve is of considerable importance, because it is the major factor in determining the choice of monitors and anaesthetic agents. While a variety of laboratory studies, including cardiac catheterization, assist in the determination of myocardial function, such information may be dated, having been undertaken several weeks to months in advance. Decisions regarding patient care should not be based upon single pressures measured at one point in time in the laboratory. A thorough history and physical examination should be undertaken before surgery, with emphasis on evaluation of the patient's cardiac reserve. Important findings include the presence or absence of dyspnoea, cyanosis, oedema, nocturia and fatigue. Exercise tolerance should be evaluated by asking questions on the patient's daily routine, rather than "How many flights of stairs can you walk?" Physical examination should determine the presence or absence of jugular venous distension, capillary

---

James B. Streisand, M.D.; K. C. Wong, M.D., Ph.D.; University of Utah School of Medicine, Salt Lake City, Utah 84132, U.S.A.

TABLE I. *New York Heart Association Classification*

Class 1	Heart disease, no symptoms
Class 2	Comfortable at rest, symptoms with ordinary activity
Class 3	Comfortable at rest, symptoms with minimal activity
Class 4	Symptoms at rest

TABLE II. *Two groups of patients with atherosclerotic cardiovascular disease*

Group 1:	Coronary artery disease but good ventricular function
	Angina pectoris is primary symptom: may have features of coronary artery spasm
	Hypertension frequently associated
	Cardiac index normal; ejection fraction > 0.55
	Left ventricular end-diastolic pressure < 12 mm Hg
	No ventricular wall motion abnormalities
Group 2:	Coronary artery disease and poor ventricular function
	Symptoms of congestive heart failure are prominent complaint
	Little or no cardiac reserve
	Previous myocardial infarction(s)
	Cardiac index 2 litre min^{-1} m^{-2}; ejection fraction > 0.4.
	Left ventricular end-diastolic pressure < 18 mm Hg
	Hypokinetic or dyskinetic (aneurysmal) segments of ventricle

filling and cyanosis. The New York Heart Association Classification may be used to help in classifying the expected cardiac performance of the patient (table I).

Patients with CAD about to undergo CABG are often classified according to the level of myocardial function. Patients with good pump function who present with angina pectoris, have no history of congestive heart failure (CHF), have ejection fractions (EF) > 0.55, and frequently are hypertensive; while those with poor ventricular function develop ischaemia as a result of CHF, have EF < 0.40, and usually have dyskinetic ventricular wall motion (table II). The incidence of perioperative problems are increased in the latter group.

Most patients with CAD also have other non-cardiac medical problems. In all but emergency CABG, these problems should be treated to optimize the patient's preoperative state. Such preparation enables the patient to withstand the perioperative period with fewer complications, and facilitates postoperative care. Medical conditions amenable to improvement are shown in table III.

TABLE III. *Medical conditions amenable to improvement before CABG surgery*

Obesity
Infections and fever
Endocrine disorders: diabetes mellitus, hypothyroidism, hyperthyroidism
Anaemia
Coagulopathies
Pulmonary: asthma, chronic bronchitis, emphysema, pneumonia
Hypertension
Psychiatric: drug dependency, alcoholism, tobacco smoking

Most patients undergoing CABG are receiving a variety of medications including β-blockers, calcium channel blockers, antihypertensive agents and digitalis glycosides. The anaesthetist should be familiar with the pharmacology of these drugs, and anticipate potential drug interactions with the anaesthetic agents planned for the surgery.

Early reports of haemodynamic instability in patients at cessation of cardiopulmonary bypass who had been taking large doses of propranolol led to the recommendation that β-blockers be discontinued 2 weeks before surgery [39]. Likewise, an early report of severe hypotension following high dose fentanyl in patients taking nifedipine resulted in the recommendation that nifedipine be discontinued 36 h before CABG (with fentanyl anaesthesia) [8]. These early reports, however, have been refuted through clinical experience. Withdrawal of propranolol led to ventricular arrhythmias, unstable angina and myocardial infarction [1,34]. A similar rebound phenomenon has been described for the discontinuation of calcium channel blockers [33]. Furthermore, clinical experience has shown that patients maintained with preoperative drug therapy have no serious haemodynamic consequences [15]. Similar considerations are true for antihypertensive agents. Clearly, the preoperative period is not the time to adjust, reduce or withdraw a patient from chronic drug therapy which has achieved maximal medical control of the patient's pathology. With rare exceptions, all chronic drug therapy should be given with a sip of water on the morning of surgery.

It is well known that certain antihypertensive agents which decrease central sympathetic outflow, such as α-methyldopa, reserpine or clonidine also decrease MAC for inhalation agents. In fact, the same may be true for the effects of certain antihypertensive agents on opioid requirements. A single dose of clonidine given orally just before surgery has been shown to reduce intraoperative fentanyl requirements by 45% and to reduce haemodynamic lability during anaesthesia for CABG [9]. Chronic propranolol therapy also reduces opioid requirements and provides a smoother intraoperative course [36]. Thus in patients receiving antihypertensive agents, changes in anaesthetic requirements (both inhalation and i.v.) must be anticipated.

As many CABG patients are receiving chronic calcium channel blocker therapy, concern has arisen regarding interactions with the volatile inhalation agents because of similar pharmacological mechanisms in producing myocardial depression and slowing of conduction through the myocardium. While animal studies using a variety of preparartions have demonstrated marked depression of ventricular function and severe bradycardia, studies in humans have shown few haemodynamic interactions [24]. Even those patients receiving a combination of calcium channel blockers and β-blockers were not observed to have conduction block during the perioperative period [24]. Thus there is no evidence that patients receiving chronic medication with calcium channel blockers are at increased risk when anaesthetized with inhalation agents. However, good clinical practice should include careful titration of the potent inhalation anaesthetics and a high degree of suspicion for adverse reactions in this group of patients.

Monitoring

Monitoring for CABG surgery includes an ECG (leads II and V_5), oesophageal stethoscope, a temperature probe, a urinary catheter, an arterial catheter and a central venous catheter. Central venous pressure (CVP) is measured from a right atrial catheter or pulmonary artery catheter. While use of the above monitoring is routine, controversy exists regarding the necessity for a pulmonary artery catheter in all CABG surgery and whether or not the central catheter should be inserted before or after the induction of anaesthesia.

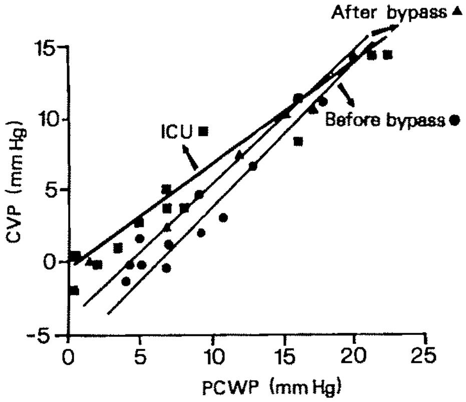


FIG. 1. Relationship between PCWP and CVP for patients with normal ventricular function. Values for PCWP correlated well with CVP over normal and abnormally high values throughout the perioperative period. Before bypass (●): $r = 0.96$ ($P < 0.001$); after bypass (▲): $r = 0.94$ ($P < 0.01$); ICU (■): $r = 0.96$ ($P < 0.001$). (Publication with permission [22].)

Mangano has shown, in patients with normal ventricular function, that changes in CVP and pulmonary artery wedge pressures are well correlated and he concluded that CVP monitoring is sufficient in this subgroup of CABG patients (fig. 1) [22]. On the other hand, haemodynamic instability may occur unexpectedly during the intraoperative and postoperative period, even in patients with normal ventricular function. The determination of cardiac output, and calculated systemic and pulmonary vascular resistances may be most helpful in the diagnosis and treatment of haemodynamic problems. In addition early detection of myocardial ischaemia may be improved by the routine use of the pulmonary artery catheter. Thus one must weigh the risks and benefits of insertion of such a catheter.

Proponents of placing a central catheter before induction state that baseline haemodynamic information is necessary for optimal care of the CABG patient. They argue that it may be necessary to "fine tune" the patient with regard to intravascular volume, inotropic support and manipulation of vascular tone [37]. While preoperative history and physical examination are important in evaluating cardiovascular function, Del Gierco has shown that 23% of patients who had been cleared for surgery by standard medical examination had severe abnormalities in cardiopulmonary function that required treatment before anaesthesia and surgery [6]. Furthermore, haemodynamic instability during induction may require precise knowledge of central pressures for optimal diagnosis and treatment. Those who place the central catheter after induction argue that, with the use of the newer synthetic opioids, haemodynamic instability is unlikely and there

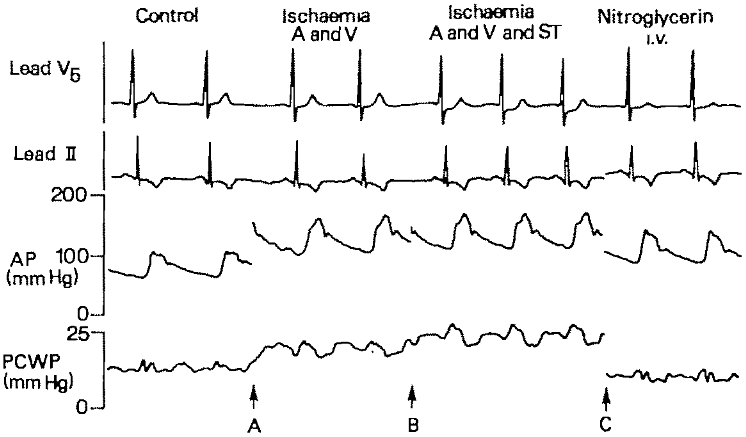


FIG. 2. Relationship between ECG ischaemic changes and PCWP. At A, with tracheal intubation, there was a marked increase in PCWP with abnormal A, C and V waves; at B, 3 min later, ST depression was evident in V_5; at C, complete resolution occurred with nitroglycerin treatment i.v. (Publication with permission [17].)

are minimal changes in central pressures during induction [7]. Not only are technical conditions for vascular cannulation less than ideal in the awake patient, but the risk of inducing myocardial ischaemia is increased. Slogoff and Keats found that 18 % of their patients arrived in the operating theatre with new ischaemic changes in the ECG despite moderate to heavy premedication, suggesting that the anxiety and stress associated with transportation to the operating suite may lead to myocardial ischaemia [35]. One can only speculate what the incidence of myocardial ischaemia might have been had a pulmonary artery catheter been placed before induction of anaesthesia. Certainly, there may be more to gain by inserting a catheter before operation in patients with poor left ventricular function, but the advantages and disadvantages must be weighed carefully before subjecting the patient to the increased risks of cannulation before induction. In our institution, the pulmonary artery catheter is generally inserted following induction of anaesthesia and tracheal intubation, but haemodynamically unstable patients (table II, group 2) frequently have one inserted in the ICU before coming to the operating theatre.

As perioperative myocardial ischaemia has been shown to produce an increase in perioperative morbidity, the detection and treatment of ischaemia cannot be overemphasized [35]. Myocardial ischaemia may occur despite good control of heart rate and arterial pressure, therefore haemodynamic indicators cannot be relied upon totally to predict myocardial ischaemia [35]. In the operating theatre, the ECG, especially lead V_5 is still relied upon to detect myocardial ischaemia. Ischaemic changes are defined as a depression of 1 mm or more in a down-sloping or horizontal ST-segment. Whilst simple and non-invasive, the ECG is insensitive and is a late detector of ischaemia. Early pathophysiological events secondary to ischaemia involve wall motion abnormalities and an increase in ventricular stiffness. Ischaemia can be detected earlier than with the ECG by using the pulmonary capillary wedge pressures and wave forms. Decreased ventricular compliance may be reflected in the PCWP tracing as an increased amplitude of the A or C waves (fig. 2). Furthermore, ischaemia of the papillary muscles, producing acute mitral regurgitation, causes very large V waves on the PCWP tracing [16].

Transoesophageal two-dimensional echocardiography has been shown to be a sensitive detector of regional ventricular wall motion abnormalities,—the earliest sign of myocardial ischaemia [5]. While this technique is too expensive for routine use at present, the non-invasive nature of the monitor and further technological refinements may make this useful and practical in the near future.

Induction and maintenance of anaesthesia (pre-bypass)

Patients with significant CAD are at great risk of ischaemia and myocardial damage during induction of anaesthesia and the period before cardiopulmonary bypass. Tracheal intubation, skin incision, sternal division and spreading, and aortic root dissection are separated by long periods when there is little stimulation. The challenge of maintaining haemodynamic stability and adequate perfusion of the vital organs is complicated by the "peaks and valleys" in somatic and sympathetic stimulation noted above.

In the early days of open heart surgery, the anaesthetist aimed to maintain the best myocardial function possible, usually using minimal doses of morphine and maintaining a "light" state of anaesthesia. Further understanding of CAD has led to a different philosophy and practice in the management of patients with CAD. It is now usual to keep myocardial function and arterial pressure depressed in a controlled manner in order to prevent increases in cardiac work and myocardial oxygen demand. Anaesthetic techniques which reduce afterload and myocardial work help to preserve myocardial oxygen supply and demand balance. These techniques utilize a variety of anaesthetic agents, but the two main classes are the opioids and the potent volatile inhalation agents. Either opioids or inhalation agents are used as the primary anaesthetic and other classes of agents are used for "fine-tuning". The following discussion examines some controversies on the use of these two major anaesthetic techniques.

Opioids have been used for cardiac surgery since the late 1960s, when Lowenstein introduced morphine anaesthesia for heart valve surgery [19]. Problems with morphine, especially for patients undergoing CABG, including hypotension, hypertension, cardiac arrhythmias and awareness during surgery, led to the introduction and extensive use of fentanyl, and more recently sufentanil, for cardiovascular surgery.

Fentanyl, in doses ranging from 30 to 150 μg kg^{-1}, has been used successfully for the majority of patients to provide a haemodynamically stable anaesthetic state, with preservation of myocardial oxygen balance. Sympathetic activation is well controlled yet, during periods of minimal stimulation, perfusion of vital organs is maintained because fentanyl causes minimal depression of myocardial function. Rather than administration by a set precalculated dose for induction of anaesthesia, fentanyl should be administered slowly, at a rate of 200–400 μg min^{-1} and titrated to the individual requirements of the patient. Anaesthesia may be maintained by administering small boluses or by continuous infusions with the aim of maintaining a constant plasma concentration of opioid, to avoid breakthrough hypertension and tachycardia.

While similar to fentanyl, sufentanil has many advantages. It is 10 times more potent than fentanyl and provides more effective blockade of haemodynamic and hormonal responses to surgical stimulation with fewer side effects [18]. In fact, when compared with fentanyl during CABG surgery, anaesthesia with sufentanil was associated with a smaller incidence of hypertension and a reduced need for supplementary agents. In addition, sufentanil has a more rapid onset of action, and titration of the drug for induction is easier. Furthermore, because of its more rapid elimination, recovery and time to tracheal extubation is significantly shorter with sufentanil compared with equivalent doses of fentanyl [18]. Thus, pending additional clinical experience, sufentanil may prove to be the opioid of choice for CABG surgery.

The use of opioids with oxygen as the sole anaesthetic for CABG is controversial [40]. Many reports of intraoperative awareness, with hypertension and increased systemic vascular resistance (SVR) have led to the use of and need for many supplementary agents [11,27]. Unfortunately, these supplements often lead to unacceptable haemodynamic depression. Benzodiazepine–opioid interactions are well known, even when the benzodiazepine is given as a premedication [2]. Nitrous oxide in combination with fentanyl increases SVR, and decreases cardiac output and arterial pressure [21]. Hyoscine may increase heart rate or cause postoperative dysphoria, both of which can adversely effect myocardial oxygen balance. Perhaps the best supplements to opioid anaesthesia are the volatile inhalation agents. When titrated carefully to avoid reducing mean arterial pressure and coronary perfusion pressure excessively, the use of halothane to supplement fentanyl 30 μg kg^{-1} provided optimal myocardial oxygenation and metabolism and haemodynamic state [25].

The use of inhalation agents as the primary agents for CABG has been advocated because of their inherent property to reduce myocardial contractility and therefore myocardial oxygen demand. Indeed, in patients with good ventricular function, Moffitt and Sethna found both halothane and enflurane maintained the myocardial oxygen supply–demand relationship and did not produce metabolic signs of ischaemia [25]. As these agents are myocardial depressants and systemic hypotensive agents, coronary perfusion pressure may be jeopardized if these agents are not titrated carefully. This may be seen particularly in patients with poor ventricular function. The practical use of inhalation agents alone may be difficult as demonstrated by Samuelson and colleagues, who required multiple adjustments of the enflurane vaporizer to maintain a steady haemodynamic state [32].

Over the past few years, isoflurane has become popular, as its primary effect is to reduce afterload with minimal myocardial depression at clinical concentrations. In addition, when compared with halothane, isoflurane causes less sensitization to catecholamine-induced arrhythmias. Furthermore, it is a coronary vasodilator and therefore attenuates coronary artery spasm, which is an important aetiological factor in ischaemia. Paradoxically, this property of isoflurane may prove detrimental to patients with coronary artery disease. A steal phenomenon has been described with isoflurane in which a reduction in blood flow to collateral-dependent, ischaemia-prone regions of the myocardium occurs as a result of increased perfusion to areas with normal coronary vasculature [3]. This phenomenon has been demonstrated clearly in canine models [4,29] but not in swine [20,23], suggesting possible species differences. In humans with CAD, Reiz and colleagues [31] found ECG and metabolic evidence of myocardial ischaemia produced by 1% end-tidal isoflurane; their measurements were obtained when MAP was reduced from 113±4 (baseline) to 68±2 mm Hg, while coronary sinus blood flow was maintained. They concluded that redistribution of myocardial blood flow by isoflurane was responsible [31]. Other results in humans suggest that isoflurane may protect against pace-induced myocardial ischaemia [38] and hypertension-induced myocardial ischaemia [10]. This controversy is discussed in greater detail elsewhere in this Symposium Issue by Reiz.

The rational approach to anaesthetizing patients for CABG probably involves a combination of opioids and inhalation agents. A basal level of opioid anaesthesia produces a stable haemodynamic state. The addition of an inhalation anaesthetic not only helps to minimize hypertension during stressful periods, but also minimizes intraoperative awareness that is unpredictable when opioids are used as the sole anaesthetic.

Cardiopulmonary bypass (CPB)

The institution of CPB results in major physiological changes in the patient and an understanding of these is crucial to optimal patient management.

Heparin should be given through a central line and its effects documented by measuring activated clotting times. When instituting CPB, signs of vena caval obstruction can be diagnosed by observing acute increases in CVP, facial swelling or scleral oedema.

The onset of CPB results in haemodilution secondary to the addition of the CPB priming solution. Correspondingly the plasma concentration of various drugs decreases. Hypothermia, non-pulsatile perfusion, exclusion of the lungs from the circulation, and alterations in protein binding affect the complex pharmacokinetics of CPB [12]. Hug and Moldenhauer demonstrated that, when fentanyl plasma concentrations decreased to less than 10 $\mu g\ ml^{-1}$, patients became responsive to sound and required diazepam supplementation, while maintaining fentanyl concentrations of 17 $\mu g\ ml^{-1}$ with a continuous infusion prevented recall [14]. Furthermore, Samuelson and colleagues demonstrated a smoother haemodynamic course post-CPB when an additional dose of sufentanil 10 $\mu g\ kg^{-1}$ was given after the onset of CPB [32].

Inhalation anaesthetics (usually isoflurane) may be used during CPB by incorporating a vaporizer in the CPB circuit. Advantages of this approach include ensuring anaesthesia and lack of patient awareness. In addition, vasodilatation can be accomplished easily by addition of inhalation agent to the CPB.

While urine output is usually greater than 1 ml $kg^{-1}\ h^{-1}$ during CPB, there is no correlation between urine output during CPB and postoperative renal failure. An occasional patient may have oliguria despite increased pump flows and large doses of diuretics. With the resumption of pulsatile flow, urine output usually resumes. A possible explanation for this phenomenon is the removal of the atrial natriuretic factor when the atria are bypassed during CPB.

The mean arterial pressure required during CPB is controversial. Probably more important for homeostasis is the maintenance of adequate flows (greater than 1.3 litre $m^{-2}\ min^{-1}$). Whilst an MAP as low as 30 mm Hg has been tolerated without adverse sequelae, a higher MAP is important in patients with carotid and cerebral vascular disease. Indeed, in these patients cerebral function should be monitored with an EEG if possible.

When discontinuing CPB, a test dose of protamine should be given. Protamine anaphylaxis produces severe refractory hypotension, often requiring large doses of adrenaline (1–5 mg) to restore circulatory homeostasis. This condition should be anticipated especially in patients who are receiving protamine insulin and those who have had a vasectomy [13]. Hyperkalaemic myocardial dysfunction may occur secondary to cardioplegia and may be treated with calcium chloride with or without glucose and insulin. Other problems impeding the smooth discontinuation of CPB include air in the coronary arteries. Functional mitral incompetence may occur acutely secondary to poor ventricular compliance. This can be diagnosed by large V waves or an inability to wedge the PA catheter and may be treated by increasing the ventricular compliance with nitroglycerin. Finally, if volume, inotropic support, and vasodilatation are unsuccessful in weaning the patient from CPB, the intra-aortic balloon pump may be used.

While vast improvements in surgical, CPB, and anaesthetic techniques have been made, significant neurological complications continue to occur after CPB. Nussmeier, Arlund and Slogoff have shown that sodium thiopentone in doses of 25–30 mg kg^{-1} given just before institution of CPB protects the human brain [28]. This was associated with increased need for inotropic support and prolonged postoperative mechanical ventilation. Also, their study was undertaken only in open ventricle procedures without hypothermia and thus further studies are required before one may recommend barbiturate therapy in all patients.

Postoperative considerations

Mechanical ventilation should be continued in the postoperative period until the following criteria are met: haemodynamic stability; minimal post-surgical bleeding; the patient is conscious and responds to commands; the patient can maintain adequate spontaneous ventilation. Early extubation (3 h after the end of surgery) can be accomplished with a reduction in cardiopulmonary morbidity and in time spent in the ICU when an inhalation anaesthetic technique is used [30]. However, these patients often require significantly greater amounts of vasodilators such as sodium nitroprusside, to control postoperative hypertension, when compared with an opioid anaesthetic technique. Under no circumstances should respiratory depression from opioids be reversed with naloxone, as severe pain, nausea, retching, vomiting and sympathetic stimulation can result, increasing the incidence of pulmonary oedema and myocardial infarction. Nalbuphine, an opioid agonist-antagonist has been shown to reverse opioid-induced respiratory depression without the adverse effects seen with naloxone and its use may lead to earlier tracheal extubation. Subsequent redevelopment of opioid depression did occur in several patients, however, requiring additional doses of nalbuphine [26].

Most patients accumulate fluid in the immediate postoperative period as a result of the perturbations of CPB, but the routine use of diuretics should be discouraged. Normal homeostatic mechanisms lead to diuresis and re-establishment of normal body fluid volumes and serum electrolyte concentrations 48–72 h following the discontinuation of surgery. Diuretics given in the early postoperative period may cause haemodynamic instability and fluid and electrolyte imbalances.

Persistent hypothermia can cause hypertension and tachycardia secondary to sympathetic stimulation. Shivering, leading to an increased myocardial oxygen demand may require the use of neuromuscular blocking drugs in critically ill patients.

REFERENCES

1. Alderman EL, Coltart DJ, Wettach GE. Coronary artery syndromes after sudden propranolol withdrawal. *Annals of Internal Medicine* 1974; **81**: 625–627.
2. Bailey PL, Wilbrink J, Zwanikken P. Anesthetic induction with fentanyl. *Anesthesia and Analgesia* 1985: **64**: 48–53.
3. Becker LC. Is isoflurane dangerous for the patient with coronary artery disease? *Anesthesiology* 1987; **66**: 259–261.
4. Buffington CW, Romson JL, Levine A, Duttlinger NC, Huang AH. Isoflurane induces coronary steal in a canine model of chronic coronary occlusion. *Anesthesiology* 1987; **66**: 280–292.
5. Clements FM, de Bruijn NP. Perioperative evaluation of regional wall motion by transesophageal two-dimensional echo-cardiography. *Anesthesia and Analgesia* 1987; **66**: 249–261.
6. Del Guercio LRM, Cohn JD. Monitoring operative risk in the elderly. *Journal of the American Medical Association* 1980; **243**: 1350–1355.
7. Dzelzkalns R, Stanley TH. Placement of the pulmonary arterial catheter before anesthesia for cardiac surgery: A

stressful, painful, unnecessary crutch. *Journal of Clinical Monitoring* 1985; **1**: 197–200.

8. Freis ES, Lappas DG. Chronic administration of calcium entry blockers and the cardiovascular responses to high doses of fentanyl in man. *Anesthesiology* 1982; **57**: A295.
9. Ghignone M, Quintin L, Duke PC, Kehler CH, Calvillo O. Effects of clonidine on narcotic requirements and hemodynamic response during induction of fentanyl anesthesia and endotracheal intubation. *Anesthesiology* 1986; **64**: 36–42.
10. Hess W, Arnold B, Schulte-Sasse U, Tarnow J. Comparison of isoflurane and halothane when used to control intraoperative hypertension in patients undergoing coronary artery bypass surgery. *Anesthesia and Analgesia* 1983; **62**: 15–20.
11. Hilgenberg JC. Intraoperative awareness during high-dose fentanyl–oxygen anesthesia. *Anesthesiology* 1981; **54**: 341–343.
12. Holley F, Ponganis KV, Stansk DR. Effect of cardiopulmonary bypass on the pharmacokinetics of drugs. *Clinical Pharmacokinetics* 1982; **7**: 234–251.
13. Horrow JC. Protamine: A review of its toxicity. *Anesthesia and Analgesia* 1985; **64**: 348–361.
14. Hug CC, Moldenhauer CC. Pharmacokinetics and dynamics of fentanyl infusions in cardiac surgical patients. *Anesthesiology* 1982; **57**: A45.
15. Kaplan JA, Dunbar RW, Bland JW, Sumpter R, Jones EL. Propranolol and cardiac surgery: A problem for the anesthesiologist? *Anesthesia and Analgesia* 1975; **54**: 571–578.
16. Kaplan JA, Wells PH. Early diagnosis of myocardial ischemia using the pulmonary arterial catheter. *Anesthesia and Analgesia* 1981; **60**: 789–793.
17. Kennedy JW, Kaiser GC, Fisher LD. Multivariate discriminant analysis of the clinical and angiographic predictors of operative mortality from the collaborative study in coronary artery surgery (CASS). *Journal of Thoracic and Cardiovascular Surgery* 1980; **80**: 876–887.
18. de Lange S, Boscoe MJ, Stanley TH, Pace N. Comparison of sufentanil–O_2 and fentanyl–O_2 for coronary artery surgery. *Anesthesiology* 1982; **56**: 112–118.
19. Lowenstein E, Hallowell P, Levine FH. Cardiovascular response to large doses of intravenous morphine. *New England Journal of Medicine* 1969; **281**: 1389–1393.
20. Lundeen G, Manohar M, Parks C. Systemic distribution of blood flow in swine while awake and during 1.0 and 1.5 MAC isoflurane anesthesia with or without 50% nitrous oxide. *Anesthesia and Analgesia* 1983; **62**: 499–512.
21. Lunn JK, Stanley TH, Eisele J. High dose fentanyl anesthesia for coronary artery surgery: Plasma fentanyl concentrations and influence of nitrous oxide on cardiovascular responses. *Anesthesia and Analgesia* 1979; **58**: 390–395.
22. Mangano DT. Monitoring pulmonary arterial pressure in coronary-artery disease. *Anesthesiology* 1980; **53**: 364–370.
23. Manohar M, Parks C. Regional distribution of brain and myocardial perfusion in swine while awake and during 1.0 and 1.5 MAC isoflurane anaesthesia produced without or with 50% nitrous oxide. *Cardiovascular Research* 1984; **18**: 344–353.
24. Merin RG. Calcium channel blocking drugs and anesthetics: Is the drug interaction beneficial or detrimental? *Anesthesiology* 1987; **66**: 111–113.
25. Moffitt EA, Sethna DH. The coronary circulation and myocardial oxygenation in coronary artery disease: Effects of anesthesia. *Anesthesia and Analgesia* 1986; **65**: 395–410.
26. Moldenhauer CC, Roach GW, Finlayson DC, Hug CC jr, Kopel ME, Tobia V, Kelly S. Nalbuphine antagonism of ventilatory depression following the high-dose fentanyl anesthesia. *Anesthesiology* 1985; **62**: 647–650.
27. Munnaneni N, Rao TL, Montoya A. Awareness and recall with high-dose fentanyl-oxygen anesthesia. *Anesthesia and Analgesia* 1980; **59**: 948–949.
28. Nussmeier NA, Arlund C, Slogoff S. Neuropsychiatric complications after cardiopulmonary bypass: Cerebral protection by a barbiturate. *Anesthesiology* 1986; **64**: 165–170.
29. Priebe H-J, Foëx P. Isoflurane causes regional myocardial dysfunction in dogs with critical coronary artery stenoses. *Anesthesiology* 1987; **66**: 293–300.
30. Quasha AL, Loeber N, Feeley TW, Ullyot DJ, Roizen MF. Postoperative respiratory care: A controlled trial of early and late extubation following coronary-artery bypass grafting. *Anesthesiology* 1980; **52**: 135–141.
31. Reiz S, Balfors E, Sorensen MB, Ariola S jr, Friedman A, Truedsson H. Isofurane—a powerful coronary vasodilator in patients with coronary artery disease. *Anesthesiology* 1983; **59**: 91–97.
32. Samuelson PN, Reves JG, Kirklin JK, Bradley E jr, Wilson KD, Adams M. Comparison of sufentanil and enflurane–nitrous oxide anesthesia for myocardial revascularization. *Anesthesia and Analgesia* 1986; **65**: 217–226.
33. Schick EC, Liang C, Heupler FA, Kahl FR, Kent KM, Kerin NZ, Noble RJ, Rubenfire M, Tabatznik B, Terry RW. Randomized withdrawal from nifedipine placebo-controlled study in patients with coronary artery spasm. *American Heart Journal* 1982; **104**: 690–697.
34. Shand DG, Wood AJJ. Editorial: Propranolol withdrawal syndrome—why? *Circulation* 1978; **58**: 202–203.
35. Slogoff S, Keats AS. Does perioperative myocardial ischemia lead to postoperative myocardial infarction? *Anesthesiology* 1985; **62**: 107–114.
36. Stanley TH, de Lange S, Boscoe MJ, de Bruijn N. The influence of chronic preoperative propranolol therapy on cardiovascular dynamics and narcotic requirements during operation in patients with coronary artery disease. *Canadian Anaesthetists Society Journal* 1982; **29**: 319–324.
37. Streisand JB, Clark NJ, Pace NL. Pulmonary arterial catheterization before anesthesia in patients undergoing cardiac surgery. *Journal of Clinical Monitoring* 1985; **1**: 193–197.
38. Tarnow J, Markschies-Horning A, Schulte-Sasse U. Isoflurane improves the tolerance to pace-induced myocardial ischemia. *Anesthesiology* 1986; **64**: 147–156.
39. Viljoen JF, Estafanous G, Kellner GA. Propranolol and cardiac surgery. *Journal of Thoracic and Cardiovascular Surgery* 1972; **64**: 826–830.
40. Wong KC. Narcotics are not expected to produce unconsciousness and amnesia. *Anesthesia and Analgesia* 1983; **62**: 625–626.

Br. J. Anaesth. (1988), **61**, 105P–118P

PROCEEDINGS OF THE ANAESTHETIC RESEARCH SOCIETY

LIVERPOOL MEETING

MARCH 25–26 1988

(The name of the author presenting the paper is shown in bold type. *Indicates non-member.)

DOSE–RESPONSE CURVES FOR SUXAMETHONIUM IN NEONATES, INFANTS AND CHILDREN

G. MEAKIN, R. D. BAKER* AND **E. P. McKIERNAN***
Department of Anaesthesia, Royal Manchester Children's Hospital, Manchester

Despite reports that paediatric patients require more suxamethonium than adults [1], there have been no definitive studies to establish the single dose–response relationships. In the present study the effective doses (ED) producing 50, 90 and 95% block were determined for neonates, infants and children during thiopentone–fentanyl–nitrous oxide anaesthesia.

Forty-five paediatric patients, 15 neonates (aged 1–28 days), 15 infants (aged 1 month–1 yr) and 15 children (aged 1–5 yr) were the subjects of the study. No premedication was given. Anaesthesia was induced with thiopentone 6–8 mg kg^{-1} and fentanyl 2–3 µg kg^{-1}, and maintained with 70% nitrous oxide in oxygen, with further thiopentone as required. Patients' tracheae were intubated without the aid of a neuromuscular blocking drug and ventilation was adjusted to maintain normocarbia. The ulnar nerve was stimulated supramaximally at the wrist using a train-of-four sequence at 2 Hz repeated every 10 s. The resulting twitch tension of the thumb was measured and recorded.

Patients from each group were randomly allocated to three sub-groups of five each, to receive suxamethonium 0.2, 0.3 or 0.4 mg kg^{-1} i.v. Linear dose–response curves were obtained by log-probit transformation of the data and the ED producing 50, 90 and 95% block obtained from the regression equations. The fitted lines were tested for parallelism and identity using the goodness-of-fit Chi squared and the *F* ratio test.

The dose-response regression lines for the three groups of patients were parallel, but the line obtained for children was significantly to the left of those for the other groups. Thus the ED for neonates and infants were significantly greater than those for children (table I).

TABLE I. *Calculated values of* ED_{50}, ED_{90} *and* ED_{95} ($\mu g\ kg^{-1}$). *N (neonates), I (infants) and C (children) indicate significant differences between the groups*

	Neonates	Infants	Children
ED_{50}	270	317	184
ED_{90}	517	608	352
ED_{95}	620	729	423
$P < 0.02$	C	—	N
$P < 0.001$	—	C	I

The ED_{90} values for all three groups were greater than that previously obtained in adults (290 µg kg^{-1}) [2]. Furthermore, the dose of suxamethonium used clinically in adults (1–1.5 mg kg^{-1}) is up to 5 times the ED_{90}, whilst that used in paediatric patients (2 mg kg^{-1}), is only 3–4 times the ED_{90} for neonates and infants. These data suggest that younger paediatric patients may require more than 2 mg kg^{-1} of suxamethonium to produce clinical effects comparable to those obtained in adults.

REFERENCES

1. Cook DR, Fischer CG. *Anesthesiology* 1975; **42**: 662–665.
2. Smith CE, Donati F, Bevan DR. *Anesthesiology* 1987; **67**: A358.

PLASMA ATRACURIUM CONCENTRATION – RESPONSE RELATIONSHIP IN PATIENTS ANAESTHETIZED WITH ISOFLURANE

C. J. R. PARKER* AND J. M. HUNTER
University Department of Anaesthesia, University of Liverpool, Liverpool

Ten healthy patients were anaesthetized with thiopentone, 66% nitrous oxide, oxygen and isoflurane. The isoflurane was adjusted to maintain a constant end-tidal concentration of 0.9%, using a Datex Capnomac. Simultaneously, the evoked electromyographic (EMG) response of the adductor pollicis to trains-of-four supramaximal stimuli at 2 Hz was recorded using a Medelec MS6 every 12.5 s. After at least 20 min, during which an EMG baseline was established and the end-tidal concentration of isoflurane stabilized, atracurium 0.25 mg kg^{-1} was administered by constant infusion over 10 min into one forearm; no further neuromuscular blocker was administered. The end-tidal isoflurane concentration was kept constant, neuromuscular blockade was not antagonized and monitoring of the EMG was continued until both first response to control (A′/A) and the train-of-four ratio (D′/A′) had recovered to more than 80%.

Following a baseline sample, venous blood was taken from the opposite arm for measurement of plasma atracurium concentration at 1, 2, 4, 6, 8, 10, 11, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 85 and 100 min after commencement of the infusion of atracurium. Plasma atracurium concentration was measured by a modification of the method described by Simmonds [1].

The plasma concentration profile was fitted to a two-compartment model (by inversely weighted non-linear least squares analysis) and pharmacokinetic parameters derived (table II). In addition, the effect on the first response of the train-of-four was fitted to a sigmoidal concentration–response curve characterized by a slope (gamma) and a midpoint (C_{p}^{ss} 50), existent within an effect compartment defined by its exit rate constant (k_{e0}) (method of Sheiner [2]).

TABLE II. *Values and SD of the pharmacokinetic and dynamic parameters*

V_1 (ml kg^{-1})	75.6	(11.5)
$T_{\frac{1}{2}}^{\alpha}$ (min)	2.86	(0.85)
$T_{\frac{1}{2}}^{\beta}$ (min)	18.45	(3.24)
$k_{21}+k_{20}$ (min^{-1})	0.110	(0.040)
C_{p}^{ss} 50 (ng ml^{-1})	356	(52)
gamma	3.48	(0.43)
k_{e0} (min^{-1})	0.118	(0.020)

The kinetic parameters showed reasonable agreement with those previously reported [3]; the dynamic parameters suggested that the C_{p}^{ss} 50 for atracurium in the presence of isoflurane is only approximately 50% of that reported by Weatherley [3] in the absence of a potent inhalation agent.

REFERENCES

1. Simmonds RJ. *Journal of Chromatography* 1985; 343: 431–436.
2. Sheiner LB, Stanski DR, Vozeh G, Miller RD, Ham J. *Clinical Pharmacology and Therapeutics* 1979; 25: 358–371.
3. Weatherley BC, Williams SG, Neill EAM. *British Journal of Anaesthesia* 1983; 55: 39S–45S.

ONSET OF NEUROMUSCULAR BLOCKADE—ALCURONIUM AND TUBOCURARINE, ALONE AND COMBINED

S. P. ROBERTS* AND B. J. POLLARD
University Department of Anaesthesia, Manchester Royal Infirmary

When certain combinations of non-depolarizing neuromuscular blocking drugs are used, the blocking effect of the mixture is greater than that which would be expected from the sum of the individual agents. Pollard [1] showed dose potentiation using alcuronium and tubocurarine. This study was designed to examine the rate of onset of this combination.

Following Ethical Committee approval 40 patients, ASA grade I or II, undergoing gynaecological or dental procedures, were selected. All received premedication with diazepam or lorazepam. Anaesthesia was induced using thiopentone, fentanyl and droperidol. Ventilation was assisted with 67% nitrous oxide and oxygen. The EMG wave form from the adductor pollicis muscle was recorded during supramaximal stimulation of the ulnar nerve at 12-s intervals (Medelec MS6 System). The train-of-four was recorded before administration of blocking drugs and for a further 3 min. The patients were randomly allocated to four groups: group A (alcuronium 0.25 mg kg^{-1}), group B (tubocurarine 0.51 mg kg^{-1}), group C (alcuronium 0.083 mg kg^{-1} plus tubocurarine 0.17 mg kg^{-1}) and group D (alcuronium 0.125 mg kg^{-1} plus tubocurarine 0.25 mg kg^{-1}). The amplitudes of the EMG wave forms were measured and the amplitude of T1 was plotted (fig. 1).

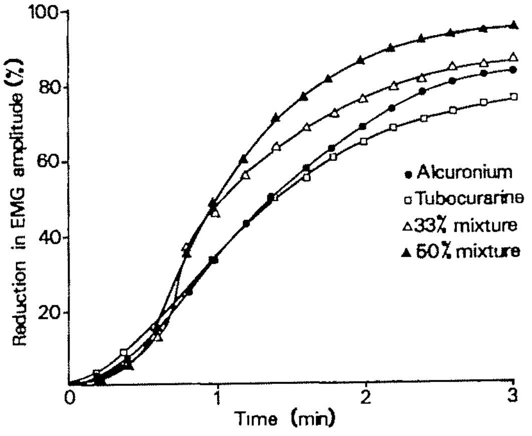


FIG. 1. Rate of onset of blockade in the four groups.

There were no significant differences between the groups with reference to age, sex or weight. There were no significant differences between groups A, B and C in rate of onset of blockade. The rate of onset of blockade in group D was significantly faster than any of the other three groups. The times to achieve 80% blockade in groups A, B, C and D were 153, > 180, 155 and 105 s, respectively.

The rate of onset of neuromuscular blockade was significantly increased using a combination of 50% of ED_{95} of tubocurarine and alcuronium when compared with either agent alone. A rate of onset equivalent to the individual agents alone was achieved using a combination of only 33% of each.

REFERENCE

1. Pollard BJ, Jones RM. *British Journal of Anaesthesia* 1983; 55: 1127–1131.

TUBOCURARINE, PANCURONIUM AND ALCURONIUM ACTION ON DIAPHRAGM AND HAND

M. C. DERRINGTON AND N. HINDOCHA
University Department of Anaesthesia, Leicester Royal Infirmary, Leicester

During upper abdominal surgery, diaphragmatic paralysis is advantageous, but neuromuscular transmission in this muscle is not monitored routinely. In order to investigate the correlation between the duration of paralysis in the diaphragm and in the forearm musculature, we have recorded evoked mechanical twitch in the diaphragm by measuring transdiaphragmatic pressure after unilateral phrenic nerve stimu-

TABLE III. *$T1_{AP}$, $T1_D$ and D_{50} (min) for each patient after tubocurarine 0.4–0.5 mg kg^{-1}, pancuronium 0.07–0.08 mg kg^{-1} of alcuronium 0.2–0.3 mg kg^{-1}*

	Patients (1–10, 11–20, 21–29)									
Tubocurarine										
$T1_{AP}$	23.9	28.0	30.0	30.3	30.9	31.4	38.6	39.7	44.7	57.0
$T1_D$	16.0	2.9	3.9	2.4	7.4	1.3	37.4	19.9	3.9	25.4
D_{50}	33.0	20.2	14.8	20.6	23.9	19.9	42.2	35.4	19.0	43.5
Pancuronium										
$T1_{AP}$	33.1	34.7	37.9	46.3	46.5	48.4	49.8	52.3	54.3	55.2
$T1_D$	9.0	14.9	13.1	17.6	19.9	21.5	25.0	22.2	30.2	30.2
D_{50}	22.3	25.7	23.8	23.9	39.6	38.9	35.1	34.4	56.4	52.8
Alcuronium										
$T1_{AP}$	28.1	28.2	34.7	41.4	45.5	46.7	47.7	49.0	55.1	
$T1_D$	3.4	17.4	14.7	11.8	8.9	32.1	15.9	32.7	18.0	
D_{50}	19.1	28.4	31.1	37.2	18.9	64.4	30.6	39.8	30.6	

lation and compared this with evoked mechanical twitch in the adductor pollicis muscle, recorded with the Myograph.

We have studied 29 healthy patients undergoing surgery for varicose veins. The patients were allocated randomly to receive tubocurarine 0.4–0.5 mg kg^{-1} (10 patients), pancuronium 0.07–0.08 mg kg^{-1} (10 patients) or alcuronium 0.2–0.3 mg kg^{-1} (nine patients). The anaesthetic technique and the method used were identical to that described previously [1]. Time to return of the first twitch of the train-of-four of the diaphragm ($T1_D$) and of adductor pollicis ($T1_{AP}$) were recorded in addition to time to 50% recovery of T1 in the diaphragm (D_{50}). These values are listed for each patient in table III.

After administration of tubocurarine there was no correlation between $T1_D$ and $T1_{AP}$ and in five patients the duration of paralysis in the diaphragm was less than 5 min; however, D_{50} was considerably longer.

In the patients who received pancuronium, there was close correlation ($r = 0.94$, $P < 0.05$) between duration of paralysis in the diaphragm and in adductor pollicis.

After alcuronium there was no correlation between the duration of paralysis in the diaphragm and adductor pollicis.

In conclusion, in the dose ranges used, pancuronium has a more predictable duration of action in the diaphragm and its use may therefore be more appropriate in upper abdominal surgery.

REFERENCE

1. Derrington MC, Hindocha N. *British Journal of Anaesthesia* 1988; **61** (in press).

TABLE IV. *% SS and % PSS before and after verapamil 0.32 mg kg^{-1} (mean ± SD).* n = 8. *$^{*}P < 0.05$; $^{**}P < 0.02$; ns = not significant*

	LV Apex		LV Base	
% SS				
Control	23.5 ± 7.7	**	18.7 ± 5.0	ns
Verapamil	19.3 ± 10.7		18.7 ± 6.8	
% PSS				
Control	5.7 ± 8.2	*	7.4 ± 12.6	ns
Verapamil	20.9 ± 23.4		8.4 ± 9.7	

EFFECT OF VERAPAMIL ON MYOCARDIAL FUNCTION IN THE PRESENCE OF FENTANYL

J. DIEDERICKS*, B. J. LEONE, D. M. PHILBIN* AND P. FOËX
Nuffield Department of Anaesthetics, Radcliffe Infirmary, Oxford

In the absence of compromised coronary blood flow, verapamil i.v., given during opioid-based anaesthesia, caused no regional dysfunction [1]. Verapamil may, however, cause marked depression of function in ischaemic myocardium [2]. This study examined the effects of verapamil in the presence of fentanyl in canine hearts with critically restricted blood flow to the apical segment of the left ventricle (LV).

Eight dogs were instrumented acutely, during 1–2% halothane anaesthesia, to permit measurement of heart rate, aortic pressure and flow, left ventricular pressure, cardiac output, stroke volume (SV), LV dP/dt, systemic vascular resistance and coronary perfusion pressure. Subendocardial wall motion was assessed by sonomicrometry in the apical and basal regions. The left anterior descending coronary artery (LAD), supplying the apical region, was dissected and a micrometer-controlled occluding snare and electromagnetic flow probe were attached to create critical constriction and to measure LAD blood flow. Halothane was discontinued and fentanyl given (100 μg kg^{-1} bolus followed by 1.5 μg kg^{-1} min^{-1}). After 40 min, critical constriction was established in the LAD and control measurements made. Verapamil 0.08, 0.16 and 0.32 mg kg^{-1} (cumulative doses) was given at 20-min intervals, and measurements taken 10–15 min after each dose. Analysis of variance and Duncan's test, and Wilcoxon matched pairs signed-rank tests were applied to the data. $P < 0.05$ was considered significant.

Verapamil depressed global haemodynamic performance significantly (mean arterial pressure −12.8%, LV dP/dt −20.8%, SV −6%, LAD blood flow −5%). Systolic shortening as a percentage of end-diastolic length (% SS) decreased, and post-systolic shortening as a percentage of total shortening (% PSS) increased significantly in the apex (table IV). Total shortening in both segments did not change.

Verapamil decreased useful contraction during ejection (% SS) and increased % PSS in an LV segment with critically compromised blood flow. The results show that verapamil, in the presence of fentanyl, increases regional asynchrony of contraction in the apical segment with limited blood supply, to such an extent that marked depression of global cardiac performance is present, even though the basal segment functions normally.

REFERENCES

1. Arvieux CC, Ramsay JG, Vidcoq M, Foëx P. *European Journal of Anaesthesiology* 1986; 3; 48–49.
2. Smith HJ, Goldstein RA, Griffith JM, Kent KM, Epstein SE. *Circulation* 1976; 54: 629–635.

PROPOFOL DECREASES SYSTEMIC VASCULAR RESISTANCE DURING CARDIOPULMONARY BYPASS

F. BOER*, P. ROS* AND J. G. BOVILL

Department of Anaesthesiology, Academic Hospital Leiden, Leiden

Cardiopulmonary bypass (CPB) is a useful experimental model for studying the isolated effects of drugs on systemic vascular resistance (SVR) [1]. We have used this model to study the effect of propofol on SVR.

After their informed consent was obtained, 28 patients scheduled for elective coronary artery surgery participated in the study, which had local Ethics Committee approval. Patients were randomly allocated to receive either propofol 2 mg kg^{-1} or an equivalent volume of its solvent. Premedication was with lorazepam 2.5–5 mg. Anaesthesia was induced with sufentanil 4–7 μg kg^{-1} followed by an infusion of sufentanil 0.05–0.1 μg kg^{-1} min^{-1}. During CPB the infusion rate was reduced to 0.025 μg kg^{-1} min^{-1}. CPB was conducted using non-pulsatile flow at 27 °C. When temperature and perfusion pressure had been stable for 5 min, 0.2 ml kg^{-1} of the test solution was given. Perfusion pressure and flow rate were registered for at least 10 min thereafter. Data were analysed using two-way ANOVA with repeated measures and *t* tests with Bonferroni's correction.

The groups ($n = 14$) were comparable with respect to age, weight, BSA, prebypass haematocrit and SVR. SVR decreased significantly ($P < 0.001$) after administration of propofol and remained signficantly lower than the control value for 8.5 min (fig. 2). There was no significant change of SVR in the solvent group.

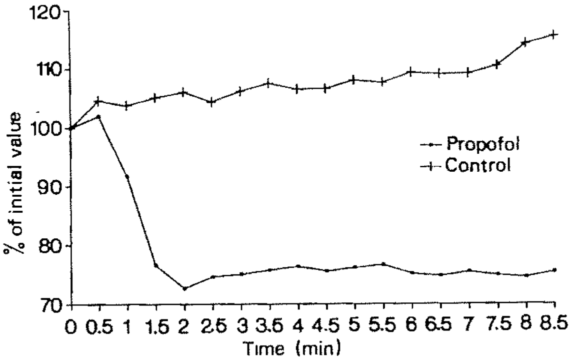


FIG. 2. Changes in SVR, expressed as percentage of control values.

The decrease of SVR after propofol 2 mg kg^{-1} during CPB was comparable to that after the administration of propofol 2 mg kg^{-1} for induction of anaesthesia [2]. This is further evidence that vasodilatation is a major contributing factor to propofol-induced hypotension.

REFERENCES

1. Videcoq M, Desmonts J-M, Marty J, Hazebroucq J, Langlois J. *Acta Anaesthesiologica Scandinavica* 1987; 31: 370–373.
2. Patrick MR, Blair IJ, Feneck RO, Sebel PS. *Postgraduate Medical Journal* 1985; 61 (Suppl. 3): 23–27.

EFFECT OF PROPOFOL-INDUCED ANAESTHESIA ON FOREARM BLOOD FLOW IN HEALTHY PATIENTS

K. McKEATING, J. P. HOWE, E. J. KEARNEY AND L. McARDLE*

Mater Infirmorum Hospital and Department of Anaesthetics, The Queen's University of Belfast

I.v. drugs used to induce anaesthesia are known to possess cardiovascular side effects. Propofol, the latest addition to this group, has been shown to possess similar activity. Dye dilution studies have indicated a decrease in cardiac output and a decrease in total systemic vascular resistance [1]. The effects of peripheral blood flow have not been examined.

It is the object of this study to measure the effect of propofol induction on forearm blood flow (FBF) and forearm vascular resistance (FVR) using mercury-in-silastic strain gauge plethysmography according to the method of Whitney [2].

With University Medical Research Ethical Committee approval and their informed consent, 20 healthy unpremedicated patients were studied. The patients were placed on the operating table and the ECG monitor attached. A 15-min rest period followed. During the study period FBF, heart rate (HR) and mean systemic arterial pressure (MAP) were obtained at 1-min intevals. Arterial pressure was recorded using a Datascope Accutorr monitor. The study period consisted of 3 min of resting, 3 min breathing 100% oxygen 8 litre min^{-1} from a Mapleson A breathing system and 3 min following the induction of anaesthesia with propofol 2.5 mg kg^{-1} given over 20 s into a large forearm vein. The readings immediately before induction (−1 min) were taken as control values. Forearm vascular resistance (FVR) was obtained by dividing the MAP by the measured FBF and recorded in R units.

Results were analysed using analysis of variance and two-tailed Wilcoxon Signed Ranks Test for matched pairs as appropriate.

There was no significant change in HR during the study period relative to the control value (mean 82 beat min^{-1}). Similarly, there was no significant alteration of FVR relative to the control value (15.9 R units).

The values for MAP and FBF were significantly altered by propofol induction (table V).

These data confirm that induction of anaesthesia using propofol causes an increase in MAP but produces little alteration in heart rate. FBF decreased significantly after propofol injection, whereas FVR increased, although not significantly.

TABLE V. *Mean ± SEM values for FBF (ml/100 ml tissue min^{-1}) and MAP (mm Hg) relative to time of injection of propofol*

	Time (min)			
	−1	+1	+2	+3
MAP	92.0±2.2	75.0±2.7	72.0±3.2	70.0±1.7
FBF	7.0±0.7	4.8±0.4	4.0±0.3	4.3– 0.2

REFERENCES

1. Coates DP, Monk CR, Prys-Roberts C, Turtle M. *Anesthesia and Analgesia* 1987; **66**: 64–70.
2. Whitney JR. *Journal of Physiology (London)* 1953; **121**: 1–27.

MOVEMENT OF THE STERNUM ON INDUCTION OF ANAESTHESIA

M. R. LOGAN AND G. B. DRUMMOND
Department of Anaesthetics, Royal Infirmary, Edinburgh

The rapid reduction in tone of ribcage inspiratory muscles on induction of anaesthesia [1] may contribute to the reduction in lung volume that occurs at this time (2). We measured cephalo–caudal movement of the sternum with a video camera (Hitachi 6P-61M) in 20 patients presenting for minor gynaecological surgery. The camera was adjusted to full zoom and suspended in a fixed position 0.9 m above the patient, to record movements of a marker located on the mid-sternum. The patient lay on a bead-filled mattress (Vac-Pac, Howmedica) which was then made rigid by suction to prevent movement of the body frame. A recording was made of 10 normal breaths, followed by induction of anaesthesia using thiopentone 2–4 mg kg^{-1}, and of 10 breaths after induction. The recording was played back on a 66-cm television screen (Barco 2634) resulting in a linear magnification of 5.4 times. Movement of the target was estimated by a single observer using a ruler. Measurements of known movements, using the same system, could be made with an accuracy of 0.2 mm (SD).

The average position of the sternal marker at end-expiration was compared, before and after induction of anaesthesia. There was no consistent direction of movement of the sternum on induction of anaesthesia, with a range from 3.1 mm cephalad to 5.4 mm caudad. However, there was a significant relationship between the direction of sternal movement and the degree of obesity of the patient (weight/ideal weight) ($r = 0.59$), such that the sternum moved caudad in overweight patients. This movement is consistent with observations we have made with other methods [3], and could be the result of a reduction in tonic inspiratory activity in muscles of the upper ribcage. Such a movement would reduce the distance between sternum and pelvis, with a corresponding reduction in lung volume.

REFERENCES

1. Drummond GB. *Anesthesiology* 1987; **67**: 695–700.
2. Bergman RA. *Anesthesiology* 1982; **57**: 14–17.
3. Logan MR, Brown DT, Newton I, Drummond GB. *British Journal of Anaesthesia* 1987; **59**: 288–294.

POSITION OF TIP OF MACINTOSH BLADE DURING LARYNGOSCOPY

W. A. HORTON*, **L. FAHY*** AND P. CHARTERS*
Department of Anaesthetics, Royal Liverpool Hospital, Liverpool

Macintosh [1] advocated positioning the tip of the curved laryngoscope blade in the angle between the base of the tongue and the epiglottis. In use, the curve of the blade often obscures a view of its tip. Others, including Stoelting [2], suggested that the tip of the blade stretches the hyo-epiglottic ligament, causing the epiglottis to move upwards. This implies that the blade tip needs to be placed below the level of the hyoid bone (as illustrated in Dunkin's paper [3]).

Local Ethical Committee approval was obtained for a study to investigate these details. Ten healthy anaesthetist volunteers (five female; mean age 32±6 yr) underwent direct laryngoscopy using 10% lignocaine spray and a "spray as you go" local anaesthetic technique. At the moment of cord visualization, a lateral x-ray was taken.

In only one subject did the x-ray show that the blade tip was positioned below the body of the hyoid; in seven subjects it was directly behind and in the other two, it was immediately above. Visualization of the cords was good in nine subjects, but not for one of the instances when the tip was above the hyoid.

The first occasion when x-ray showed the blade tip was above the hyoid was quite unexpected because laryngoscopy was straightforward, with good cord visualization. The second time it was obvious during the laryngoscopy because the blade tip was noted to slip suddenly upwards as pressure was applied via the laryngoscope handle. Failure to display the cords at this juncture was considered noteworthy because a previous anaesthetic history had shown no difficulty with laryngoscopy.

These findings warrant further investigation. It would appear that optimal placement of the Macintosh blade tip is immediately behind or below the body of the hyoid.

REFERENCES

1. Macintosh RR. *Lancet* 1943; 1: 205.
2. Stoelting RK. In: Miller RD, ed. *Anesthesia*. New York: Churchill Livingstone, 1981; 233–242.
3. Dunkin LJ. *British Journal of Hospital Medicine* 1980; **23**: 77–80.

TOWARDS AUTOMATIC CONTROL OF GENERAL ANAESTHESIA WITH ENFLURANE

H. M. ROBB*, A. J. ASBURY, W. M. GRAY AND D. A. LINKENS*
University Department of Anaesthesia, Western Infirmary, Glasgow and University Department of Engineering, Sheffield

Clinical signs are used as guidelines for the administration of anaesthetic drugs. Our ultimate objective is to devise a computer control system, operating from rules based on clinical signs, to produce an individually tailored anaesthetic state. The aim of this study was to assess the usefulness of systolic arterial pressure (SAP) as an index of anaesthetic depth for such a system.

A proportional-integral control system was set up with an RML 380Z-D computer interfaced to a Dinamap and an enflurane vaporizer controller [1]. A program was designed to maintain the patient's SAP at 90% of that predicted by age and sex. A minimum dose of 0.6% enflurane was given for the first 10 min and the user instructed to give morphine 0.05 mg kg^{-1} if the delivered dose of enflurane exceeded a pre-set limit. This rule could only be activated once in 15 min.

Following Ethical Committe approval, 21 patients (ASA I or II) were studied. After premedication with temazepam 10–20 mg and ranitidine 150 mg, anaesthesia was induced with thiopentone 3–5 mg kg^{-1} and morphine 0.1 mg kg^{-1}. Neuromuscular blockade was maintained with vecuronium. The patients were ventilated with 66% nitrous oxide in oxygen. Enflurane and morphine were administered by, or on instruction from, the controller. Nine clinical signs were recorded every 5 min as PRST score [2].

No patient complained of awareness. For statistical analysis the patients were divided into those who required extra morphine (group B) and those who did not (group A). There was no intergroup statistical difference in age, weight or duration of operation. Results are shown in table VI.

TABLE VI. *Results. TSAP = Target SAP; TPR = time to patient response; VAP = inspired concentration; RMSD = root mean square deviation about TSAP; PRST = PRST score. (Mean values ± SD).* *P < 0.05 *by Wilcoxon's sum of ranks test*

	Group A (n = 14)		Group B (n = 7)
TSAP (mm Hg)	118.8±7.7		114.4±7.2
TPR (min)	4.8±1.9	*	10.0±3.7
HR (beat min^{-1})	67.3±7.8	*	82.9±16.6
SAP (mm Hg)	118.1±8.1		119.9±8.4
VAP (%)	1.1±0.7	*	2.0±0.5
RMSD	7.0±2.8	*	9.4±2.3
PRST	0.46		0.96

In conclusion, it seems that, within the limits of this study the rules applied, which technically control SAP, produce a pattern of clinical signs recognizable as general anaesthesia.

REFERENCES

1. Nieman M, Richardson W, Gray WM, Asbury AJ. *Journal of Medical Engineering Technology* 1987; 11: 34–36.
2. Evans JM, Bithell JF, Vlachonikolis IG. *British Journal of Anaesthesia* 1987; 59: 1346–1355.

COMPUTERIZED ANALYSIS OF CONTINUOUS PULSE OXIMETRY FOR PROLONGED PERI-OPERATIVE STUDIES

R. G. WHEATLEY*, D. SOMERVILLE AND J. G. JONES
York District Hospital, and University Department of Anaesthesia, Leeds

The respiratory effects of general anaesthesia and analgesic regimens have previously been based on intermittent observations of ventilatory rate or arterial blood-gas tensions. Pulse oximetry, however, has enabled clinicians to monitor arterial oxygen saturation (Sa_{O_2}) continuously. Earlier work using off-line analysis has demonstrated that episodes of significant hypoxia ($Sa_{O_2} < 85$) may occur in sleeping patients receiving continuous i.v. infusions of opioids in the post-operative period.

A system is described which provides a rapid analysis and display of the pattern of Sa_{O_2} with time over prolonged periods of study. This is suitable for clinical research, being portable, robust and easy to use at the patient's bedside. The Nellcor N-100 pulse oximeter is interfaced with an IBM-compatible PC and a 20-megabyte Winchester Hard Disc. Every 10 s the oximeter sends a 30-character string to the computer which displays it on the monitor screen. The display includes the Sa_{O_2}, heart rate, oximeter and alarm status and the time of recording. Every 10 s the screen is updated and a cumulative record is made of the number of 10-s epochs at a given Sa_{O_2}. The data are automatically written to a file on the Hard disc (24-h of data = 380000 bytes). At the end of the study period the data file is rapidly analysed.
The data are analysed in three ways:

Hypoxic episodes. The number, duration and time of occurrence of hypoxic episodes during the study can be identified.

Hourly distribution of Sa_{O_2}. The system automatically prints out all the Sa_{O_2} values recorded during each hour, together with the mean hourly Sa_{O_2}.

Compressed spectral array. The distribution of Sa_{O_2} in each hour can be displayed as a spectrum of Sa_{O_2} values against time.

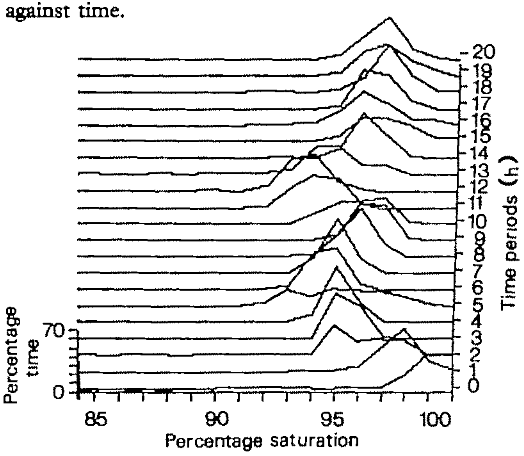


FIG. 3. Compressed spectral array from a patient recovering from general anaesthesia.

A compressed spectral array from a patient (ASA Class I) recovering from general anaesthesia for gynaecological surgery is shown in figure 3. The study commenced 1 h (zero time) after the end of surgery. The array shows a characteristic displacement to the left of Sa_{O_2} values, secondary to the administration of i.m. morphine. A recovery phase is seen, followed by further displacement secondary to subsequent doses of i.m. morphine.

A MODEL FOR DIFFERENT MODES OF FORCED OSCILLATION IN THE RESPIRATORY SYSTEM DURING HIGH FREQUENCY JET VENTILATION

E. S. LIN, B. E. SMITH, M. J. JONES* AND S. D. MOTTRAM*
University Department of Anaesthesia, Leicester Royal Infirmary, Leicester

Gas exchange during high frequency ventilation is dependent on complex fluid dynamic mechanisms and their effects on gas distribution [1]. These are poorly understood and not easily accessible to monitoring in a clinical situation. However, gas exchange during HFJV will also be related to the overall mechanical response of the respiratory system to the pulses of gas from the ventilator. This response is frequency dependent and can be monitored using relatively simple methods.

Recent theoretical and animal studies suggest that the respiratory system behaves as a simple second order system or damped oscillator in the range of ventilation frequencies encompassed clinically by HFJV. Anaesthesia was induced with etorphine 0.05 ml kg^{-1} and maintained with alphaxalone–alphadolone 10 ml h^{-1}. Mechanical gain and input–output phase shift response curves derived from airway pressure and thoracic strain gauge measurements, indicate that the respiratory system can be driven into resonance at the fundamental ventilation frequency [2, 3].

The present studies were designed to investigate the possibility of more complex modes of oscillation occurring in the respiratory system. Domestic pigs with body weights 19–25 kg were anaesthetized and subjected to HFJV. Measurements of thoracic and abdominal excursions were made using strain gauges and airway pressure and cardiovascular parameters were recorded.

A comparison of thoracic and abdominal movement waveforms showed an increasing phase lag with ventilation frequency, the excursions being in phase at lower frequencies and tending towards 180° as the frequency increased. Mechanical gain responses indicate the presence of an additional peak at lower frequencies than predicted by taking a simple second order system model. A model is presented to explain the results in terms of the mechanical interaction between the components of the respiratory system and the inertance of the abdominal contents.

REFERENCES

1. Drazen JM, Kamm RD, Slutsky AS. *Physiological Reviews* 1984; **64**: 505–543.
2. Lin ES, Smith BE. *British Journal of Anaesthesia* 1987; **59**: 256–264.
3. Lin ES, Smith BE. *British Journal of Anaesthesia* 1987; **59**: 661P.

USE OF SCAVENGING FACILITIES AND OCCUPATIONAL EXPOSURE TO WASTE ANAESTHETIC GASES

P. A. STONE*, A. J. ASBURY AND W. M. GRAY
Department of Anaesthetics and University Department of Anaesthesia, Western Infirmary, Glasgow

In pollution surveys in Glasgow, anaesthetists' exposure to nitrous oxide was found to vary between hospitals, with the number of samples exceeding 100 p.p.m. ranging from 31 to 91%. We suspected that an important factor contributing to the variation might be the extent to which the available scavenging equipment was actually used.

A confidential questionnaire was sent to 199 anaesthetists working in eight Glasgow hospitals, to investigate their use of scavenging equipment.

The survey response rate was 67%. Scavenging equipment was fitted in the operating theatres of all the hospitals, but in the anaesthetic rooms of only 50%. Available scavenging equipment was more frequently used in the operating theatre than in the anaesthetic room, and there was more variation in its use in the anaesthetic room. The mean use (range) in the operating theatre was 95 (0–100)% ($n = 133$) while the mean use in the anaesthetic room was 79 (0–100)% ($n = 113$). The reported use of scavenging by consultants was similar to other grades, in the anaesthetic room and in the operating theatre. In the four hospitals where pollution surveys had been carried out the fraction of scavenged theatre sessions appeared to be negatively correlated with the mean nitrous oxide exposure of the anaesthetists.

Fifty-three percent of anaesthetists gave reasons for not using scavenging equipment and 74% of reasons related to equipment design and integration. Problems included scavenging a Magill system, awkwardness of scavenging tubing and valves, and noise. Other reasons included difficulty in using scavenging in specific circumstances such as inhalation induction or with a T-piece in children.

We have not been able to demonstrate a clear relationship between the use of scavenging equipment and nitrous oxide exposure. The survey has, however, revealed deficiencies which are reducing the use of scavenging equipment, and some of these could be remedied by improved design and the use of alternative systems.

EFFECTS OF AGE ON THE PHARMACODYNAMICS OF ALFENTANIL DURING BREAST SURGERY

H. J. M. LEMMENS*, J. G. BOVILL, P. J. HENNIS AND A. G. L. BURM*
Department of Anaesthesiology, University Hospital Leiden, Leiden

A study of the pharmacodynamics of alfentanil based on EEG changes, suggested that the elderly are more sensitive than younger patients to the CNS effects of alfentanil [1]. We studied the effects of age on the relationship between plasma concentration of alfentanil and response to peri-operative stimuli in two groups: 14 patients aged between 31 and 55 yr (mean ± SD, 44 ± 7 yr) and 14 patients aged between 55 and 86 yr (70 ± 10 yr). All patients were female, ASA I–II, undergoing curative breast surgery for breast cancer. Alfentanil was administered by a computer-driven infusion pump

(TIAC). Anaesthesia was induced with 66% nitrous oxide in oxygen and a target plasma concentration of alfentanil 350 ng ml^{-1}, to be achieved in 2 min. When consciousness was lost, suxamethonium 1 mg kg^{-1} was given and the lungs ventilated with 66% nitrous oxide in oxygen. Four minutes later the trachea was intubated and the target concentration of alfentanil was decreased to 200 ng ml^{-1}. If, during surgery, the patient exhibited signs of inadequate anaesthesia, defined as an increase in systolic arterial pressure by more than 15 mm Hg above normal, a heart rate higher than 90 beat min^{-1}, other autonomic signs or somatic responses, the target plasma concentration was increased by 50–100 ng ml^{-1}. If the patient did not respond during a 15-min period, the target concentration was decreased by 50 or 100 ng ml^{-1}. In order to identify somatic responses, minimal doses of pancuronium were used. Arterial blood samples, for determination of plasma concentrations of alfentanil, were taken before any change of the target concentration and 4 min after a new target concentration was achieved. Blood samples were also taken before intubation, skin incision and extubation or, when naloxone was required to achieve adequate spontaneous ventilation, 10 min after stopping nitrous oxide. Plasma concentrations were determined by capillary gas chromatography. Plasma concentration *v.* probability of no response curves for intubation, skin incision and the probability of needing naloxone in both groups, and for the surgical procedure in each patient, were fitted by logistic regression.

The plasma concentration for which the probability of no autonomic or motor response was 50% (C_P50) was, in the young and old group respectively, 440 and 441 ng ml^{-1} for intubation; 226 and 196 ng ml^{-1} for skin incision; and 272 and 226 for the probability of needing naloxone. The average C_P50 for the surgical operation was 255 ± 90 ng ml^{-1} in the young group and 280 ± 133 ng ml^{-1} in the older group. This difference was not statistically significant. The duration of anaesthesia in the young and older group was 154 ± 29 min and 154 ± 25 min, respectively. The average alfentanil requirement in the young group was 2.21 ± 0.68 mg kg^{-1} min^{-1}, and 1.68 ± 0.52 mg kg^{-1} min^{-1} in the older group. This difference in dose requirement was statistically significant ($P < 0.05$).

We conclude that age has no effect on the pharmacodynamics of alfentanil in women undergoing breast surgery.

REFERENCE

1. Scott JC, Stanski DR. *Journal of Pharmacology and Experimental Therapeutics* 1987; **240**: 159–166.

A PHYSIOLOGICAL MODEL FOR THE DISTRIBUTION OF INJECTED AGENTS, WITH SPECIAL REFERENCE TO PETHIDINE

N. R. DAVIS AND **W. W. MAPLESON**
Department of Anaesthetics, University of Wales College of Medicine, Cardiff

The model exists as a Fortran program, based on Mapleson's [1] circulation-time model, with compartments for lungs, peripheral shunt, kidneys, portal bed, liver, other viscera, lean, fat, sample brain, and i.m. injection site. All blood is stored in pools: an arterial pool, pre- and post-injection central venous pools, and portal, lean and fat peripheral venous pools. Perfusion-limited distribution is achieved by moving stroke volumes of blood around the model and equilibrating them with the tissues in the compartments.

Intracellular and extracellular fluids are separately represented in each compartment and in blood. In each fluid, four forms of the agent are distinguished: un-ionized dissolved in water ("standard" form), ionized dissolved in water, un-ionized dissolved in lipid, and bound to protein. Equations define the equilibrium between these four forms in any one fluid. For equilibration between a bolus of blood and the tissue in a compartment, the total amount of agent in the blood and tissue is distributed between the four fluids so that the concentration in standard form is the same in all of them. Hepatic metabolism and renal excretion were represented by simple extraction fractions from incoming blood to the relevant compartments, with the renal fraction being a function of urinary pH.

Quantification of the physiological aspects was taken from Davis and Mapleson [2] and of the physico-chemical properties of pethidine from Davis [3]. The latter were derived, somewhat uncertainly, from the literature plus experimental measurement of saturable protein binding in plasma, erythrocytes and muscle cells. Other protein was assumed to behave as plasma protein.

Reasonable agreement between model predictions and four experimental studies of single i.v. injections was obtained after adopting the second most likely estimate of the lipid/standard-form partition coefficient. Agreement with data from two studies of i.m. injections was obtained after giving the i.m. injection site a perfusion twice that of the lean compartment. In this form, the model satisfactorily matched data for a 24-h i.v. infusion, and for repeat i.m. injections over 28 h.

ACKNOWLEDGEMENT

This work was supported by the Medical Research Council.

REFERENCES

1. Mapleson WW. *British Journal of Anaesthesia* 1973; 45: 319–334.
2. Davis NR, Mapleson WW. *British Journal of Anaesthesia* 1981; 53: 399–405.
3. Davis NR. *The Pharmacokinetics of Injected Analgesics.* Ph.D. Thesis, University of Wales 1987.

COMPARISON OF RATE OF ONSET OF RESPIRATORY DEPRESSION AFTER I.V. MORPHINE OR DIAMORPHINE

F. J. ANNAN*, D. RAY* AND G. B. DRUMMOND
Department of Anaesthetics, Royal Infirmary, Edinburgh

Diamorphine is more lipid soluble than morphine; this may increase its speed of action as well as its potency. After i.m. administration, diamorphine is 1.6–2.6 times more potent [1]. Speed of action is important in dose interval choice, particularly when i.v. administration is by "titration" or on demand.

We studied 30 patients about to have routine surgery under general anaesthesia, using a randomized design, excluding those with overt respiratory disease, more than 20% overweight, or who had recently received halothane. Premedication was with diazepam 10 mg by mouth, anaesthesia was

TABLE VII. *Respiratory effects of morphine and diamorphine (mean ± SD)*

	Morphine	Diamorphine
Minimum V_T (% control)	65 ± 14	42 ± 22
Minimum f (% control)	76 ± 12	52 ± 16
Time to 70% V_T (min)	1.40 ± 0.47	1.75 ± 0.41
Decrease in f (min)	2.57 ± 0.82	3.93 ± 1.93

induced with thiopentone 4–6 mg kg^{-1} i.v., and intubation was facilitated with suxamethonium i.v. End-tidal carbon dioxide concentration (Engstrom Eliza), expired tidal volume (Magtrak respirometer), and airway pressure (Furness FC10 transducer) were recorded on a chart recorder (Transamerica Visilight). The patients breathed 1% halothane in 67% nitrous oxide in oxygen from a T-piece system, supplied with fresh gas at a flow rate of 7.5–10 litre min^{-1}, adjusted so that minimum $F\text{I}_{CO_2}$ was about 0.5%. After 10 min of stable ventilation, control measurements were made for 3 min. Each patient then received either diamorphine hydrochloride 2.5 mg or morphine sulphate 5 mg i.v. and recordings were made for a further 10 min. Mean V_T, frequency (f), and $F\text{E}'_{CO_2}$ were measured at 15-s intervals. Four patients became apnoeic, all after diamorphine. Of the remaining patients, the greatest reduction in tidal volume and ventilatory frequency were measured. To estimate the rate of onset of these effects, the time at which 70% of this reduction had occurred was noted. At the time 70% of the change in tidal volume had occurred, no patient had a increase in $F\text{E}'_{CO_2}$ greater than 0.6 kPa, despite reductions in minute volume of up to 62%. Table VII indicates that, in these circumstances, diamorphine is more than twice as potent than morphine, that the rate of onset of depression of tidal volume is more rapid than of frequency, but that there is no difference between the times of 70% maximal depression after diamorphine or morphine (Mann–Whitney U test).

REFERENCES

1. Kaiko RF, Stanley LW, Rogers AG, Grabinski PY, Houde RW. *New England Journal of Medicine* 1981; **304**: 1501–1505.

EFFECTS OF DOPAMINE ON GASTRIC PRESSURE

R. SARGINSON*, CERI GREEN*, R. DUCKWORTH, M. HARTLEY*, N. PARR* AND I. T. CAMPBELL
University Departments of Anaesthesia and Surgery, Royal Liverpool Hospital, Liverpool

Dopamine is an endogenous catecholamine which is used pharmacologically at low doses (2 µg kg^{-1} min^{-1}) to protect renal function and at doses of 5 µg kg^{-1} min^{-1} and greater for myocardial support. Low dose dopamine is frequently given to critically ill patients over prolonged periods as a prophylactic measure against acute renal failure. Dopamine has been shown to produce gastric relaxation and thus to delay gastric emptying when infused into dogs at 2.5 µg kg^{-1} min^{-1} and in man at 9 µg kg^{-1} min^{-1} for 25 min [1]. We have studied the effect of dopamine on gastric relaxation in normal human volunteers at doses of 2 µg kg^{-1} min^{-1} for 150 min.

Gastric corpus fundus pressure was measured using a micro pressure transducer contained in the distal end of a nasogastric tube within an 800-ml plastic bag passed into the stomach. The bag was inflated with air at a rate of 800 ml min^{-1} for 30 s. Gastric pressure was measured during filling and over a further 150 s. Average pressure during inflation was derived from the area under the curve during the filling period (dynamic P) and during the following 150 s with the balloon inflated (static P).

The subjects were five healthy males aged 29–41 (median 32) yr. All studies followed an overnight fast. After 30 min rest, following insertion of the bag, gastric pressure (dynamic and static P) was measured three times at 15-min intervals, then after 15, 30 and 45 min of dopamine (in 5% dextrose) infusion at 2 µg kg^{-1} min^{-1}. A further series of measurements were made after 120, 135 and 150 min of dopamine infusion. The results were compared with the same measurements made during the infusion of a corresponding volume of 5% dextrose alone over the same time period.

During dextrose-only infusion, gastric pressure did not alter. During dopamine infusion, both dynamic and static P decreased and were significantly less at 15–45 min of infusion than during dextrose infusion (dynamic pressure: 9.9 ± 1.0 *v.* 14.6 ± 0.8 cm H_2O ($P < 0.01$); static pressure 9.1 ± 1.1 *v.* 13.6 ± 0.5 cm H_2O ($P < 0.01$)). At 120–150 min of infusion, gastric pressures in three subjects decreased further, but in two subjects it recovered to preinfusion values, so that the differences between the dopamine and dextrose groups was not significant.

It is concluded that dopamine 2 µg kg^{-1} min^{-1} produces gastric relaxation over the first 1 h of infusion. This may delay gastric emptying. During 120–150 min of infusion, gastric relaxation in some individuals persists, but in others gastric pressures return to normal. Prolonged dopamine infusion at 2 µg kg^{-1} min^{-1} may delay gastric emptying in some patients and may thus cause difficulties in nasogastric feeding.

REFERENCE

1. Valenzuela J, Lin D. *Scandinavian Journal of Gastroenterology* 1982; 17: 293–296.

PREOPERATIVE FLUIDS, RANITIDINE AND OPIOID–ATROPINE PREMEDICATION

J. R. MALTBY, **A. EWEN**, N. KOEHLI AND L. STRUNIN*
Department of Anaesthesia, Foothills Hospital at the University of Calgary, Calgary

In healthy unpremedicated patients, 150 ml of oral fluid 2–3 h before surgery does not increase residual gastric volume (RGV) at induction of anaesthesia; oral ranitidine 150 mg with the oral fluid decreases both volume and acidity [1]. Opioid analgesics delay gastric emptying and drug absorption [2] and may therefore increase RGV in patients given oral fluids and reduce the effectiveness of oral ranitidine. In this study we measured RGV and pH in patients who received preoperative oral fluids and ranitidine, followed by opioid–atropine premedication.

One hundred and twenty patients, ASA physical status I or II, aged 18–70 yr, scheduled for elective surgical procedures, were randomly allocated to one of four groups. Two to three

TABLE VIII. *Duration of fast, residual gastric volume (RGV) and pH in group 1 (water+marker dye+placebo, no opioid), group 2 (water+marker dye+placebo+opioid), group 3 (oral fluid+placebo+opioid) and group 4 (oral fluid+ranitidine+opioid).* ***P < *0.001 compared with groups 2–4 (ANOVA)*

		Fast (h)		RGV (ml)		pH	
Group	*n*	Mean	SD	Mean	Range	Mean	Range
1	30	14.6	1.7	23.9*	0–90	3.0	1.7–7.7
2	30	14.0	1.5	13.1	0–70	3.0	1.5–7.8
3	29	2.7	0.8	16.6	0–133	3.4	1.7–7.3
4	31	2.6	0.6	16.6	0–51	5.3	1.5–7.4

hours before surgery, each patient ingested 10 ml water containing phenol red 50 mg as a marker dye with placebo alone (groups 1 and 2), placebo with oral fluids 150 ml (water, tea, coffee or fruit juice) (group 3) or oral ranitidine 150 mg with oral fluid 150 ml (group 4). Patients in group 1 (control) received no opioid premedication. Those in groups 2, 3 and 4 received morphine 7.5–15 mg i.m. or pethidine 50–100 mg i.m., with atropine 0.6 mg 1 h before surgery. Following induction of anaesthesia, the gastric contents were aspirated through an 18-gauge Salem sump tube. Volume was recorded and pH was measured with a Corning pH meter.

The groups were comparable with respect to sex, age and weight. The preoperative fasting period, RGV and pH in each group are shown in table VIII.

Opioid–atropine premedication i.m. did not increase the mean RGV of patients who received oral fluids 1 h earlier. Mean RGV of patients in group 1 was significantly increased compared with that in groups 2–4. Oral ranitidine increased the pH to more than 2.5 in 90% of the patients in group 4. We conclude that there is no evidence that healthy patients should not be permitted oral fluids until 3 h before elective surgery.

REFERENCES

1. Maltby JR, Sutherland AD, Sale JP, Shaffer EA. *Anesthesia and Analgesia* 1986; 65: 1112–1116.
2. Todd JG, Nimmo WS. *British Journal of Anaesthesia* 1983; 55: 1189–1193.

PLASMA GLUCOSE DURING INDUCED HYPOTENSION

A. M. C. COOPER AND P. J. MORRIS
Department of Anaesthesia, Addenbrooke's Hospital, Cambridge

Experimental hypotensive anaesthetic techniques have been shown to produce hyperglycaemia [1], as does haemorrhage. This investigation examined the changes in blood glucose concentration during hypotension induced by three different methods, including haemorrhage and isoflurane.

Thirty-two adult mongrel cats were anaesthetized, the trachea intubated and the lungs ventilated to normocapnia. Anaesthesia was maintained with 65% nitrous oxide and 1.5% halothane in oxygen and vecuronium bromide infused at 0.15 mg kg^{-1} h^{-1} in maintenance fluid consisting of Hartmann's solution 4 ml kg^{-1} h^{-1}. Surgical preparation consisted of bilateral cannulation of femoral vessels, a parietal burr hole and dural incision, followed by implantation of cortical microelectrodes used in a parallel study.

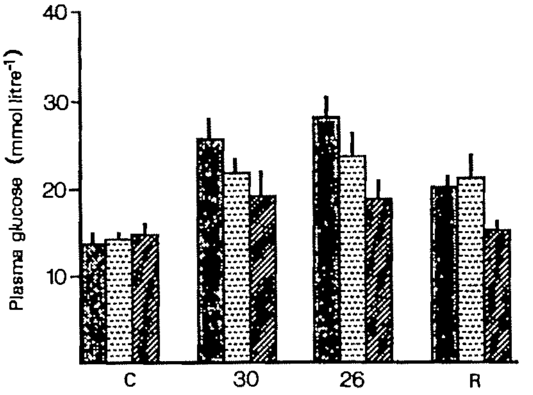


FIG. 4. Plasma glucose concentrations (+SE) in groups 1, 2, 3 (respectively, sets of columns). C = control; 30 = MAP 30 mm Hg; 26 = MAP 26 mm Hg; R = 30 min after hypotension.

The inspired concentration of halothane was reduced to 0.6% and the animals randomly allocated to receive one of the following techniques to induce hypotension: group 1, sodium nitroprusside infusion up to a maximum of 1 mg kg^{-1} with blood withdrawal; group 2, isoflurane up to a concentration necessary to achieve a mean arterial pressure (MAP) of 45 mm Hg, followed by blood withdrawal; group 3, isoflurane alone. All animals received practolol 0.4 mg kg^{-1}. MAP was reduced at 5 mm Hg min^{-1} to 30–32 mm Hg for 30 min, then to 26–28 mm Hg for 15 min. Hypotensive drugs were then discontinued and withdrawn blood reinfused. Arterial blood samples were taken, for analysis of plasma glucose [2], before hypotension, after 30 min at 30–32 mm Hg, at the end of hypotension and 30 min after hypotension. Results are presented in figure 4.

In the groups in which blood withdrawal was involved, plasma glucose concentration increased during hypotension to exceed 20 mmol $litre^{-1}$ in 21 of 22 animals. This increase was not prevented in group 2 by inspired isoflurane concentrations of 2.5–3%. In nine of the 10 animals in group 3 (no blood withdrawn) the plasma glucose concentration remained less than 20 mmol $litre^{-1}$ during hypotension and recovered to control values within 30 min of restoration of arterial pressure. This may have clinical implications, as hyperglycaemia is a risk factor in the development of cerebral ischaemia [3].

REFERENCES

1. Morris PJ, Heuser D, McDowall DG, Hashiba M, Myers D. *Anesthesiology* 1983; 59: 10–18.
2. Trinder P. *Annals of Clinical Biochemistry* 1969; 6: 24–27.
3. Pulsinelli, WA, Waldman SW, Rawlinson D, Plum F. *Neurology* 1982; 32: 1239–1246.

ARTERIAL OXYGEN DESATURATION FOLLOWING ADMINISTRATION OF 50% NITROUS OXIDE

P. N. REED*, C. J. WILKINS* AND
A. R. AITKENHEAD
University Department of Anaesthesia, Leicester

Preliminary observations of haemoglobin oxygen saturation (Sa_{O_2}) during labour showed that desaturation occurred following the administration of Entonox. Possible explanations include diffusion hypoxia [1], central respiratory depression and absorption atelectasis. The present study was undertaken in normal volunteers to investigate this phenomenon.

Ten healthy volunteers aged 25–35 yr gave informed consent to be studied. Each subject breathed, in sequence, gas mixtures comprising 50% nitrogen in oxygen, 50% nitrous oxide in oxygen, or room air. Each mixture was inhaled under conditions of maximum voluntary hyperventilation for 2 min and normal ventilation for 10 min. Following each period of gas administration, measurements were continued for 15 min whilst the subject breathed room air. Subjects then rested for 5 min before breathing the next mixture. The sequence of administration of gas mixtures was varied randomly between individuals.

Subjects breathed via a closely fitting modified CPAP mask incorporating inspiratory and expiratory valves (but without application of CPAP). A mass spectrometer sampled from the mask to afford continuous monitoring of inspired and expired gas composition (oxygen, carbon dioxide, nitrous oxide and nitrogen). Sa_{O_2} was measured with a Nellcor pulse oximeter applied to a finger and expired minute volume was recorded using an electronic Wright's respirometer.

Minimum values for Sa_{O_2} and end-tidal oxygen concentration ($F\text{E}'_{O_2}$) and mean values for $F\text{E}'_{CO_2}$, $F\text{E}'_{N_2O}$, $F\text{E}'_{N_2}$ and minute volume were recorded for each of the 15-min periods following the respiratory manoeuvres. Statistical analysis was by paired Wilcoxon signed rank tests and paired *t* tests, as appropriate.

Following normal ventilation with nitrous oxide in oxygen, Sa_{O_2} was signficantly lower than following nitrogen in oxygen for all but 1 min of the first 12 min of the recovery phase. Following the hyperventilation sequences, Sa_{O_2} decreased for each gas mixture. However, the depression of Sa_{O_2}' was greatest both in magnitude and duration following hyperventilation with nitrous oxide in oxygen, least following hyperventilation with nitrogen in oxygen and intermediate following hyperventilation with air (table IX). Comparisons of the recovery phases for the three gas mixtures showed no differences in the end-tidal carbon dioxide concentrations.

TABLE IX. *Minimum Sa_{O_2} and time below baseline Sa_{O_2} (mean SD) following each respiratory manoeuvre. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$ compared with both other groups*

Respiratory pattern	Gas mixture	Minimum Sa_{O_2} (%)	Time below baseline Sa_{O_2} (s)
Hyperventilation	Air	90.1±4.4*	382±188
	N_2/O_2	93.0±2.8*	334±255
	N_2O/O_2	85.6±7.6*	558±192***
Normal ventilation	Air	97.2±1.2	—
	N_2/O_2	96.4±1.3	158±224**
	N_2O/O_2	94.0±2.0**	511±201**

We conclude that, after inhalation of nitrous oxide in oxygen, a significant hypoxaemia is produced in normal subjects.

REFERENCE

1. Sheffer L, Stefferson JL, Birch HA. *Anesthesiology* 1972; 37: 436–439.

SEDATION OF MECHANICALLY VENTILATED PATIENTS IN THE ITU: COMPARISON OF ISOFLURANE WITH MIDAZOLAM

K. L. KONG*, S. M. WILLATTS* AND
C. PRYS-ROBERTS
Sir Humphry Davy Department of Anaesthesia, University of Bristol, Bristol

We have compared isoflurane with midazolam for sedating mechanically ventilated patients in the intensive care unit.

Thirty-two patients (aged 26–78 yr) who required mechanical ventilation were admitted to the trial. Their APACHE II scores were between 0 and 26. Patients with head injury or uncontrolled bleeding were excluded. They were randomly allocated to be sedated with either 0.1–0.6% isoflurane in an air–oxygen mixture or a continuous i.v. infusion of midazolam 0.01–0.2 $\text{mg kg}^{-1}\text{ h}^{-1}$. The dose of sedative was adjusted to maintain a pre-determined level of sedation for as much of the time as possible. At this level, the patients were tranquil, co-operative or easily rousable. Incremental i.v. doses of morphine 0.05 mg kg^{-1} were given for analgesia as judged either by communication with the patient or by autonomic signs. Sedation was assessed initially and hourly thereafter, on a nominal scale modified from Ramsay and colleagues [1]. The study was limited to a maximum of 24 h. The trial sedative was stopped either when the patient was judged ready for weaning from ventilatory support, or at 24 h (whichever was earlier). Thereafter, the times to response to command and to extubation were recorded. If sedation was required beyond 24 h, an alternative scheme of sedation was substituted after these recovery times had been assessed. One patient in the isoflurane group died after 7 h of sedation. Six of 18 patients who received isoflurane and eight of 14 patients who received midazolam were resedated on an alternative scheme of sedation after 24 h.

The two groups of patients did not differ with regard to age, weight, APACHE II scores and duration of sedation.

Patients who received isoflurane were satisfactorily sedated for a mean 84.4% (range 46–100%) of the trial period. Those who received midazolam were sedated at the desired level for a mean 55.9% (range 8–85%) of the time. This difference was statistically significant ($P < 0.001$). The mean total doses of morphine administered in the two groups of patients were similar: isoflurane group, mean 13.8 mg (range 0–77 mg); midazolam group mean 11.7 mg (0–41 mg). All patients sedated with isoflurane and nine of the 14 patients sedated with midazolam moved their toes to command within 10 min of discontinuation of sedation. The median time to extubation was 60 min for the isoflurane patients (range 0–135 min) and 109.5 min for the midazolam patients (range 50–289 min).

REFERENCE

1. Ramsay MAE, Savege TM, Simpson BRJ, Goodwin R. *British Medical Journal* 1974; 2: 656–659.

POSTER PRESENTATIONS

RESPIRATORY FUNCTION AFTER MAJOR HIP SURGERY

R. GANTA*, R. DUCKWORTH, D. CHILDS, S. V. JAGADEESH* AND I. T. CAMPBELL
University Department of Anaesthesia, Royal Liverpool Hospital, Liverpool

Many patients are transiently hypoxaemic after anaesthesia and surgery for a variety of reasons, including diffusion hypoxia and hypoventilation as a result of depletion of carbon dioxide stores [1]. Hypoxaemia persisting beyond the immediate postoperative period is seen after abdominal surgery and is said to result from disturbances in the ventilation–perfusion relationship at the base of the lung produced by a decrease in functional residual capacity caused by pain and spasm of the abdominal muscles [2]. Extensive abdominal surgery involving intestinal resection, however, produces more severe hypoxaemia than more limited abdominal surgery such as cholecystectomy [3]. To test the hypothesis that the extent of surgery might affect postoperative hypoxaemia, respiratory function has been studied in patients undergoing elective major hip surgery. This involves extensive tissue damage and blood loss, but does not involve the abdominal wall.

Arterial Po_2, Pa_{CO_2} and vital capacity (VC) were measured before operation, 1 day after operation and 7 days after operation in 10 patients (four male) undergoing elective hip surgery (mean (±SEM)) age 62.4 (±3.9) yr. The same measurements were made on 13 patients (six male) (56.3±4.6 yr) undergoing upper abdominal surgery for cholecystectomy ($n = 11$) or vagotomy and drainage ($n = 2$). All patients were anaesthetized using a thiopentone–neuromuscular blockade analgesia technique, supplemented as necessary with an inhalation agent. Morphine i.m. was used for postoperative analgesia. Eight hip patients received blood transfusions (2 (0–4) units), but none of the abdominal group.

Arterial Po_2 decreased the first day after hip surgery ($P < 0.01$) then increased on day 7 ($P < 0.05$) (table X). Vital capacity decreased on day 1 then increased to day 7 ($P < 0.01$). After upper abdominal surgery, Pa_{O_2} showed the well established pattern of a decrease on day 1 ($P < 0.001$), increasing on day 7 ($P < 0.001$). VC decreased on day 1 ($P < 0.001$), increasing on day 7 ($P < 0.01$). Arterial Pco_2 did not alter in either group.

TABLE X. *Changes in arterial oxygen and vital capacity*

	Before op.	Day 1	Day 7
Hip surgery			
Pa_{O_2} (kPa)	10.8±0.5	9.8±0.5	11.0±0.5
VC (litre, BTPS)	2.64±0.29	2.11±0.25	2.74±0.30
Abdominal surgery			
Pa_{O_2} (kPa)	12.0±0.2	9.6±0.4	11.2±0.3
VC (litre, BTPS)	2.44±0.26	1.10±0.3	1.95±0.30

It is concluded that patients undergoing major elective hip surgery are mildly hypoxaemic 1 day after surgery and that this hypoxaemia is associated with a decrease in VC. It is possible that the cause of the hypoxaemia is a reduction in lung volume, but the cause of this reduction is not known.

REFERENCES

1. Hewlett AM, Branthwaite MA. *British Journal of Anaesthesia* 1975; 47: 102–107.
2. Alexander JI, Spence AA, Parikh RK, Stuart B. *British Journal of Anaesthesia* 1973; 45: 34–40.
3. Morton A, Ebert B. *Anesthesia and Intensive Care* 1974; 2: 175–178.

INFLUENCE OF INTRAOPERATIVE ACUPUNCTURE AND DROPERIDOL ON POSTOPERATIVE EMESIS

J. W. DUNDEE*, K. R. MILLIGAN AND A. C. McKAY
Department of Anaesthetics, The Queen's University of Belfast and Belfast City Hospital

Postoperative nausea and vomiting is a distressing complication of general anaesthesia and may delay the discharge of patients undergoing otherwise minor procedures. Electro-acupuncture, when given with nalbuphine premedication, has been shown to have an anti-emetic action comparable to that of cyclizine [1]. The purpose of this study was to investigate the intraoperative use of electro-acupuncture as a means of reducing postoperative nausea and vomiting when a rapidly acting opioid is given. Approval for the study was obtained from the University Medical Research Ethical Committee.

Ninety healthy, unpremedicated women aged 18–55 yr, undergoing minor gynaecolgical surgery were randomly allocated to one of three equal groups. Anaesthesia was induced with alfentanil 7 $\mu g\ kg^{-1}$ followed by methohexitone 2 $mg\ kg^{-1}$ and maintained by 67% nitrous oxide in oxygen supplemented by increments of methohexitone 10 mg and alfentanil 100 μg as required. During the operation the patients received either 5 min of electro-acupuncture at the P6 point [2] using a frequency of 10 Hz, droperidol 2.5 mg i.v. or no intraoperative treatment (control groups). After operation the patients were visited by a "blinded" observer who assessed the incidence of emetic sequelae.

There were no differences between the groups with regard to age, weight, duration of anaesthesia or the total dose of

TABLE XI. *Numbers (and percent) of patients with postoperative emetic symptoms.* *$P < 0.05$ *compared with other groups*

Time after op. (h)	Control	ACP	Droperidol
0–1	8 (28%)	9 (30%)	2 (7%)*
1–4	10 (33%)	8 (28%)	5 (17%)

drugs administered. The results are summarized in table XI. There were fewer emetic sequelae when droperidol was given than in the other two groups which were almost identical in the incidence of sickness.

The results of this study indicate that the intraoperative use of electro-acupuncture is ineffective in preventing the nausea and vomiting associated with an anaesthetic technique which used alfentanil and methohexitone. They are similar to those recently reported by Weightman and his colleagues [3]. Further studies are being undertaken to ascertain if this is attributable to the timing of the acupuncture or to the pharmacokinetics of the particular opioid used.

REFERENCES

1. Ghaly RG, Fitzpatrick KTJ, Dundee JW. *Anaesthesia* 1987; **42**: 1108–1110.
2. Lynas AGA, Chestnutt WN, Dundee JW, Ghaly RG. *British Journal of Clinical Pharmacolgy* 1986; **22**: 223P.
3. Weightman WM, Zacharias M, Herbison P. *British Medical Journal* 1987; **295**: 1379–1380.

AUTOMATIC CONTROL OF ARTERIAL PRESSURE AFTER CARDIAC SURGERY WITH GLYCERYL TRINITRATE AND SODIUM NITROPRUSSIDE

J. R. COLVIN* AND G. N. C. KENNY
University Department of Anaesthesia,
Glasgow Royal Infirmary, Glasgow

Hypertension after cardiac surgery increases blood loss, endangers suture lines and may have a detrimental effect on myocardial oxygen balance. It is usually managed by the infusion of short acting vasodilators.

Glyceryl trinitrate (GTN) may have advantages over sodium nitroprusside (SNP) in terms of its effect on the pulmonary [1] and coronary circulations [2], although its efficacy in the management of the early hypertension after cardiopulmonary bypass is not clearly established.

The use of a closed-loop computer system to control the infusion of a vasodilator has been shown to compare favourably with manual control [3]. We have developed a closed-loop system for the ATARI 1040ST microcomputer to control arterial pressure by the simultaneous infusion of two vasodilators. This system is designed to deliver GTN in increasing doses up to a maximum of 50 mg h^{-1} in response to a systolic arterial pressure greater than the target pressure. If this fails to bring the pressure under control, the second automatic infusion introduces SNP in a similar incremental manner. The target pressure is prescribed by the surgical staff and entered into the computer, which stores cardiovascular and infusion information every 1 min, thus allowing detailed and unbiased assessment of the therapy. The control program is based on that described by Reid and Kenny [3].

This "dual pump" system has been used in a preliminary study, with GTN and SNP to control arterial pressure in 24 patients requiring vasodilators after cardiopulmonary bypass. The patients were assessed in terms of those controlled by GTN alone and those requiring the addition of SNP.

Assessment of arterial pressure control over 5 h revealed that 14 of the patients were controlled by GTN alone and 10 required supplementary SNP. There were no significant differences in age, weight, six or target pressure between these two groups.

Since GTN alone cannot control hypertension in some patients after cardiac surgery, the use of an automated dual pump system is a useful method of administering GTN and SNP simultaneously.

REFERENCES

1. Azar I, Turndorf H. *American Review of Respiratory Disease* 1979; **119** (Suppl.): 92.
2. Estafanous FG, Tarazi RC. *The American Journal of Cardiology* 1980; **46**: 685–694.
3. Reid JA, Kenny GNC. *British Journal of Anaesthesia* 1987; **59**: 247–255.

IS IT NECESSARY ALWAYS TO USE THE RIGHT FOREARM FOR ACUPUNCTURE ANTIEMESIS?

K. T. J. FITZPATRICK*, J. W. DUNDEE,
R. G. GHALY AND C. C. PATTERSON
Departments of Anaesthetics and Medical Statistics, The Queen's University of Belfast

In our various acupuncture/acupressure (ACP) antiemetic studies [1, 2] we have followed the traditional Chinese practice and stimulated the right P6 (Neiguan) point. We questioned whether we should use the right or the dominant hand, so during the past year we have asked patients whether they are normally right- or left-handed, and analysed the efficacy of ACP in each category (table XII).

TABLE XII. *Incidence of sickness in right- and left-handed patients all having stimulation of the right P6 point*

	Dominant hand			
	Right		Left	
	Not sick	Sick	Not sick	Sick
Acupuncture				
Postop. vomiting	101	30	9	5
Cancer chemotherapy	121	49	13	6
Transcutaneous stimulation				
Postop. vomiting	58	22	4	3
Acupressure				
Morning sickness	111	45	6	5
Totals	391	146 (27%)	32	19 (37%)

On questioning, only 7.5% of 1000 inpatients admitted to being left-handed. This is similar to our study group and, because of this low percentage, we have pooled groups as far as was justified.

Although, when applying Cochrane's Analysis of Pooling [3], we found a significantly greater efficacy of ACP anti-emesis in right-handed patients, the difference is so small and the incidence of left-handedness so low, that it can be ignored in clinical practice.

REFERENCES

1. Dundee JW, Chestnutt WN, Ghaly RG, Lynas AGA. *British Medical Journal* 1986; **293**: 583–584.
2. Dundee JW, Fitzpatrick KTJ, Ghaly RG. *Anesthesiology* 1987; **67**: A165.
3. Armitage P. *Statistical Methods in Medical Research.* Oxford: Blackwell Scientific Publications, 1971.

DIGITAL PLETHYSMOGRAPHY DURING GENERAL ANAESTHESIA: COMPARISON OF TWO TECHNIQUES

J. P. HOWE, D. A. ORR, E. J. KEARNEY AND L. McARDLE*
Mater Infirmorum Hospital and Department of Anaesthetics, The Queen's University of Belfast

Photoplethysmography is widely used as a non-invasive monitor of cardiovascular function during anaesthesia. The apparatus consists of a light emitter/detector which is placed on the patient's finger, the output signal being amplified and displayed on an oscilloscope as the pulse volume waveform. The amplitude of the pulse volume (PVA) varies extensively during anaesthesia in response to alterations in cardiovascular dynamics.

Mercury strain gauge plethysmography, on the other hand, is a quantitative method of measuring peripheral blood flow based on the detection of volume changes in human limbs as described by Whitney [1].

The object of the study was to examine the correlation between the outputs from a photoplethysmogram and a strain gauge plethysmogram when sited on adjacent fingers during general anaesthesia.

Twelve ASA I and II patients scheduled for elective surgery under general anaesthesia requiring normocapnic intermittent positive pressure ventilation were studied, following informed verbal consent and medical research Ethical Committee approval. The anaesthetic sequence consisted of benzodiazepine premedication, thiopentone induction, vecuronium bromide for neuromuscular blockade and isoflurane maintenance.

Following induction a spring-loaded digital plethysmogram (Hewlett–Packard 15230A) was sited on the distal phalanx of the index finger and a mercury-in-rubber strain gauge plethysmogram correspondingly sited on the adjacent middle finger. The output from both devices was amplified and recorded on a dual channel recorder at a paper speed of 1 cm s^{-1} (Electroplan 120).

Paired recordings of PVA (mm) and digital blood flow (DBF) (ml/100 ml tissue min^{-1}) were taken at 5-min intervals until the conclusion of surgery. Results were analysed by regression analysis.

A total of 235 matched recordings of PVA and DBF were obtained from 12 patients. PVA ranged from 3 to 39 mm and DBF from 1 to 71 ml blood/100 ml tissue min^{-1}.

Analysis yielded values for the 12 patients ranging from $r = -0.64$ to $r = 0.86$. The correlation coefficient for the pooled data ($n = 235$) was $r = 0.37$.

These data suggest that, in general, changes in displayed PVA during anaesthesia are not indicative of changes in digital blood flow. There are individual patients in whom a high degree of correlation between the two parameters may be obtained (eg. $r = 0.86$), but it is not possible to identify them without concurrent strain gauge plethysmography.

REFERENCE

1. Whitney JR. *Journal of Physiology* (*London*) 1953; **121**: 1–27.

Br. J. Anaesth. (1988), **61**, 119–124

CORRESPONDENCE

BLOCKED EAR AFTER EXTRADURAL INJECTION—A CLARIFICATION

Sir,—I thank Hardy [1] for his comments on my previous letter. I shall clarify two points and cite some of the experimental data, as asked.

I believe that the cause of the early endolymphatic hydrops syndrome is low *relative* perilymph pressure. Hence Hardy's remarks on high baseline cerebrospinal fluid (CSF) pressures, for example in pregnancy, are irrelevant. What is important is a sudden decrease in CSF pressure (from any resting value) that cannot be compensated for by normal cochlear fluid mechanisms. In other cases with weight loss or dehydration, there may be chronic CSF hypotension. The high pressure theory cannot explain how endolymphatic pressures exceed CSF or perilymph pressures, as undoubtedly occurs in Menière's disease.

My theory applies to the very early stages of Menière's disease. Later, it is difficult to predict intralabyrinthine pressures as cochlear membranes and fluid spaces become permanently distorted and long-term compensation may occur.

Perilymph pressures in animals have been altered indirectly by surgical manipulation of pressures in the middle ear [2], inner ear [3] and CSF [3, 4]. Reduced pressures led to a large sustained decrease in cochlear function which was not seen when pressures were increased [2]. Low pressures were stable, but high pressures decreased slowly, suggesting that the cochlear aqueduct can act as a one-way valve. Increased CSF pressure usually caused hydrops if round windows ruptured (although only in acute and not chronic specimens) and a collapsed endolymph system if not [3]. This confirms that low perilymph pressures cause hydrops, and high pressures result in some membrane compression. Large increases in CSF pressure which evidently did not rupture round windows did not affect cochlear activity [4].

I hope anaesthetists will take up Hardy's plea for futher research in this area. If so, they should concentrate on normal patients rather than those with previous ear disease, and provide more details than did Hardy on his latest patient. Specific enquires should be made for all symptoms of early hydrops (deafness, tinnitus, audiosensitivity, fullness, vertigo, fluctuation), their exact time course, laterality and symmetry. Situations should be chosen where there is no ambiguity on whether or not pressures are high or low. Eardrum displacement is a sensitive indicator of labyrinthine pressure and this promises to be a very useful non-invasive way of monitoring CSF pressure [5].

A. G. Gordon
London

REFERENCES

1. Hardy PAJ. Blocked ear after extradural injection. *British Journal of Anaesthesia* 1987; **59**: 667.
2. Ohmura M, Satoh H, Honjo I. Influence of altered middle ear pressure on cochlear microphonics. *Acta Otolaryngolica* 1987; **104**: 255–260.
3. Nomura Y, Hara M. Experimental perilymphatic fistula. *American Journal of Otolaryngology* 1986; **86**: 267–275.
4. Matsuura S, Kuno M, Nakamura T. Intracranial pressure and auditory evoked responses of the cat. *Acta Otolaryngologica* 1986; **102**: 12–19.
5. Marchbanks RJ, Reid A, Martin AM, Brightwell AP, Bateman D. The effect of raised intracranial pressure on intracochlear pressure: three case studies. *British Journal of Audiology* 1987; **21**: 127–130.

ROUTINE USE OF ATROPINE IN OBSTETRIC ANAESTHESIA

Sir,—Dr May and colleagues [1] stated "... we are unaware of any evidence that a single dose of suxamethonium is likely to cause bradycardia". Permit me to draw their attention to the papers listed below [2–6]. In reference [5] alone, 20 cases of severe bradycardia, including 12 cases of cardiac asystole following a single injection of suxamethonium are presented. Of special interest to Dr May and colleagues is that one of these patients (No. 6) was a 34-year-old healthy woman undergoing emergency Caesarean section.

J. Viby-Mogensen
Herlev

REFERENCES

1. May AE, Theophilus SWJ, James RH. Routine use of atropine in obstetric anaesthesia. *British Journal of Anaesthesia* 1988; **60**: 243–244.
2. Johnstone M. Relaxants and the human cardiovascular system. *Anaesthesia* 1955; **10**: 122–138.
3. McLesky CH, McLeod DS, Hough TL, Stallworth JM. Prolonged asystole after succinylcholine administration. *Anesthesiology* 1978; **49**: 208–210.
4. Wong AL, Brodsky JB. Asystole in an adult after a single dose of succinylcholine. *Anesthesia and Analgesia* 1978; **57**: 135–136.
5. Sørensen M, Engbæk J, Viby-Mogensen J, Guldager H, Molke-Jensen F. Bradycardia and cardiac asystole following a single dose of suxamethonium. *Acta Anaesthesiologica Scandinavica* 1984; **28**: 232–235.
6. Inoue K, Reichelt W. Asystole and bradycardia in adult patients after a single dose of suxamethonium. *Acta Anaesthesiologica Scandinavica* 1986: **30**: 571–573.

Sir,—Thank you for the opportunity to reply to Dr Viby-Mogensen's letter. We stated that we were unaware of any evidence that a single dose of suxamethonium is *likely* to cause bradycardia, not that it has *never* been known to do so.

The incidence of bradycardia following suxamethonium is difficult to determine, as many of the older papers included cases where a second dose of suxamethonium was given. Some more modern papers have failed to state categorically that no second dose of suxamethonium was used. In others, there is a possibility that residual suxamethonium remaining in the tail of an indwelling needle has been flushed into the circulation or that the effects of other drugs or surgical stimulus have not been excluded. Nevertheless, we are sure that very rare idiosyncratic bradycardia may occur with suxamethonium. This is true of other drugs, and Dr Morgan in his reply to our original letter [1] pointed out the rare bradycardias of vecuronium (a drug which we do not use for Caesarean section—the competitive muscle relaxant in the early half of the series was alcuronium, while the one more recently used was atracurium). Despite this, the use of atropine has disappeared from routine anaesthetic practice in non-obstetric general anaesthesia.

In the series of 20 cases of bradycardia following suxamethonium that Dr Viby-Mogensen mentions [2] there are a number of interesting aspects. First, only one case involved Caesarean section, therefore the problem we address is not that which is particularly associated with Caesarean section. Second, as two of the patients had received atropine i.v. at induction, clearly, its use is of dubious value. Third, 18 of the 20 patients received fentanyl at induction, and this may have contributed to the problem; i.v. opioids are used rarely in obstetric anaesthesia. Fourth, despite their department's collection of a large number of cases, they still do not deem it necessary to administer atropine before operation.

The argument of our original letter is that, when atropine has been abandoned for routine use in general anaesthesia, there is even less indication for its routine use in obstetric anaesthesia. We stand by that position and feel that our large series supports this view.

A. E. May
S. W. J. Theophilus
R. H. James
Leicester

REFERENCES

1. Morgan M. Routine use of atropine in obstetric anaesthesia. *British Journal of Anaesthesia* 1988; **60**: 244.
2. Sorensen M, Engbek J, Viby-Mogensen J, Guldager H, Molke Jensen F. Bradycardia and cardiac asystole following a single injection of suxamethonium. *Acta Anaesthesiologica Scandinavica* 1984; **28**: 232–235.

HEPATOTOXICITY AFTER GENERAL ANAESTHESIA

Sir,—Hussey and colleagues [1] have recently reported evidence of liver damage following inhalation anaesthesia. Currently we are investigating postoperative hepatocyte injury using an alternative marker of liver disease, the serum F protein concentration. Although our preliminary results confirm that volatile anaesthetics are often associated with hepatic damage, we have found that the injury presents several days later than previously described. We have also observed a paradoxical improvement in hepatic function in patients with preoperative liver damage.

We have studied 12 previously healthy adults undergoing minor surgical procedures with uncomplicated inhalation anaesthetics (10 received halothane, one received enflurane and one received isoflurane). The postoperative serum F protein concentration (measured 24 h after surgery) did not change significantly (paired *t* test) from preoperative values. The serum F protein concentration is a very sensitive test of liver damage; it shows a close correlation with the histological assessment of hepatocellular damage, and the concentration is increased in patients such as the elderly who have minimal hepatic disease (unpublished data). Our failure to confirm the occurrence of early postanaesthetic liver damage may result from the small number of patients studied and the relatively insensitive statistical techniques used. However, it may indicate that postoperative changes in GST represent enzyme induction rather than hepatocellular damage.

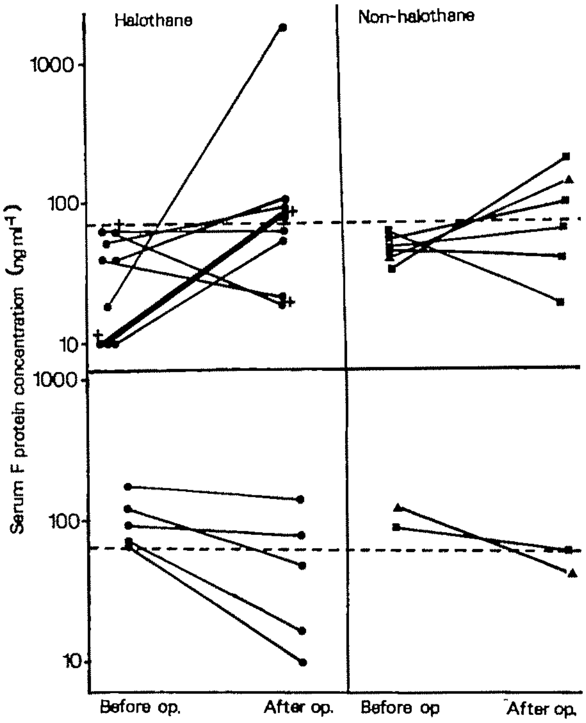


FIG. 1. Top graphs: Serum F protein concentration (log scale) before and after operation (day 6) in patients receiving inhalation anaesthetic agents. Patients with preoperative liver disease (lower graphs) were suffering from drug induced liver disease (two), alcohol abuse (one), carcinoma (one) or had no known cause of liver damage (two). Broken lines indicate upper limit of normal for serum F protein concentration. ● = Halothane; ▲ = isoflurane; ■ = enflurane. +● = Two inhalation anaesthetics used during the same operation.

Previous studies of postoperative liver damage have found evidence of hepatic injury several days after exposure [2]. We have studied 22 patients, receiving uncomplicated inhalation anaesthesia 6 days after exposure. In the 15 patients with normal preoperative liver function (serum F protein concentration < 60 ng ml^{-1}) the serum F protein concentration was increased after operation in 10 and this change was observed with all anaesthetic agents studied (fig. 1, top graphs). In seven patients with preoperative liver disease (serum F protein concentration > 60 ng ml^{-1}) there was a significant decrease in the postoperative serum F protein concentration (fig. 1, bottom graphs). The reason for this different response is unclear—it is unlikely to represent an improvement in hepatic function resulting from the stay in hospital, as the changes were observed in patients with carcinoma, in whom liver function is unlikely to benefit from drug or alcohol withdrawal. It may result from improvement in hepatic blood flow in patients with minor liver disease, or from alteration in hepatic enzyme activity causing hepatotoxic metabolites to be formed less readily when the liver has suffered previous injury.

Our preliminary results confirm that postanaesthetic liver injury is common. The time at which this injury develops remains to be determined, and further studies are required to establish the mechanism and significance of the observed biochemical abnormalities.

G. R. FOSTER
P. BOWNESS
K. HOLDER
D. B. G. OLIVEIRA
London

REFERENCES

1. Hussey AJ, Aldridge LM, Paul D, Ray DC, Beckett GJ, Allan LG. Plasma glutathione S-transferase concentration as a measure of hepatocellular integrity following a single general anaesthetic with halothane, enflurane or isoflurane. *British Journal of Anaesthesia* 1988; **60**: 130–135.
2. Akdimen SA, Flanagan TV, Landmesser CN. Serum glutamate transaminase changes following anesthesia with halothane, methoxyflurane and other inhalational anesthetic agents. *Anesthesia and Analgesia* 1966; **45**: 819–825.

POTENTIAL PROBLEMS OF USING BOTH OPIOIDS AND LOCAL ANAESTHETIC

Sir,—We are taught that opioids cause respiratory depression, and indeed they do, both in volunteers who are not in pain and in pain-free animals. In practice, significant postoperative clinical respiratory depression is not a common problem when opioids are titrated against pain. The reason for the difference between the experimental and clinical contexts is the presence or absence of pain. Those working in the field of chronic pain are aware of this difference. Patients taking appropriate doses of oral morphine for management of opioid-sensitive pain are troubled by constipation, not by respiratory depression. A patient taking opioids (without respiratory depression) whose pain is then relieved by another measure, such as a neurolytic block, will succumb to respiratory depression unless the dose is reduced [1]. After successful procedures, it is important to reduce the opioid for this reason [2].

Where opioids are used in postoperative care, there are several situations in which ignorance of this balance between pain and dose of opioid has the potential for disaster. If a patient who has been given opioids without satisfactory pain relief, but with no clinical respiratory depression, is subsequently given extradural local anaesthetic (or local anaesthetic by any other route), the balance between pain and those earlier doses of opioid is altered, and clinical respiratory depression may occur.

Intrathecal opioids used for perioperative pain relief are administered commonly at induction rather than titrated against pain. The optimum dose may vary and, unless dose-response relationships are understood, the dose given may be excessive. If the local anaesthetic results in good pain relief while using local anaesthetic and opioid simultaneously, there is no pain to balance the dose of opioid. The widely quoted respiratory depressant effect of intrathecal opioids [3] involved just such a local anaesthetic–opioid mixture.

In the unfortunately common situation where use of extradural local anaesthetic cannot be continued for logistic reasons, absorption of opioid from i.m. injection may be delayed if the injection is given into muscles still "covered" by the extradural. In patients receiving a lumbar extradural block and a gluteus maximus injection, the time of the mean peak plasma morphine concentration was 90 min ($n = 10$) [4], compared with a mean time of peak concentration of 15 min (SEM 2.3) ($n = 5$) [5] after deltoid injection of 10 mg in volunteers. Such delayed absorption (and effect) is analogous to that in the shocked patient in whom i.m. injection results in a reservoir of drug which is released when muscle blood flow increases.

The clinical message is that the dose of opioid should be titrated against pain.

H. J. MCQUAY
Oxford

REFERENCES

1. Hanks GW, Twycross RG, Lloyd JW. Unexpected complication of successful nerve block. *Anaesthesia* 1981; 36: 37–39.
2. Kanner RM, Foley KM. Patterns of narcotic drug use in a cancer pain clinic. *Annals of New York Academy of Sciences* 1981; **362**: 161–172
3. Davies GK, Tolhurst-Cleaver CL, James TL. Respiratory depression after intrathecal narcotics. *Anaesthesia* 1980; **35**: 1080–1083.
4. Kay N, Allen CM, Bullingham RES, Baldwin D, McQuay HJ, Moore RA, Price RK, Sear JW. Influence of meptazinol on metabolic and hormonal responses following major surgery. *Anaesthesia* 1985; **40**: 223–228.
5. Stanski DR, Greenblat DJ, Lowenstein E. Kinetics of intravenous and intramuscular morphine. *Clinical Pharmacology and Therapeutics* 1978; **24**: 52–59

SINGLE BREATH INDUCTION OF ANAESTHESIA WITH ISOFLURANE

Sir,—The recently published article by Lamberty and Wilson [1] raises some interesting questions. The use of isoflurane in the single vital capacity breath technique has been reported previously [2, 3], although additional i.v. fentanyl was administered in an attempt to suppress the airway irritability associated with the use of isoflurane.

Lamberty and Wilson used a concentration of 2 % isoflurane which, they claimed, was selected on empirical grounds, but proved subsequently to be satisfactory. It would be useful to known on what grounds a concentration of 2 % was selected, and what criteria were used to determine the suitability of this concentration. There is some evidence to suggest that the concentration of isoflurane required can be determined by extrapolation from the data of Ruffle and colleagues [4]. These authors assessed the inspired halothane concentrations required to produce amnesia and unresponsiveness in an oxygen–halothane induction system. The required concentrations were 1.5% (2 MAC) and 3.3% (4.4 MAC), respectively, and it was suggested that the addition of 70% nitrous oxide to the system could reduce the inspired concentration for unresponsiveness to 1.5% (2 MAC). Following this argument, the MAC equivalent concentration of isoflurane would be 2.3%—a value similar in magnitude to that used by Lamberty and Wilson. This assumes that the MAC value of isoflurane in this age group is 1.15% [5], rather than the figure of 1.28% quoted by the authors.

The authors have demonstrated that isoflurane is suitable for use in the single breath induction technique, but they did not report the induction time. Mean induction times observed have varied from 112 s with 4% halothane in oxygen [6], 83 s with 4% halothane and 70% nitrous oxide in oxygen [7] to 38 s with 5% isoflurane in oxygen supplemented by fentanyl 5 $\mu g\ kg^{-1}$ [3]. A pilot study carried out in our department has recorded a mean induction time of 80 s with 2.5% isoflurane and 70% nitrous oxide in oxygen. This suggests that the addition of nitrous oxide to the gas mixture, and the use of isoflurane, are factors which shorten induction time, although direct comparison with the study of Loper and colleagues [3] is difficult because of the use of i.v. fentanyl in that study. Nonetheless, it would be valuable to learn what induction times were achieved by Lamberty and Wilson.

The authors state that patients were interviewed after operation and were asked for a description of recall of induction. It is not stated if this process was conducted in a blinded fashion. It would be difficult to conduct a study of this nature assessing induction characteristics in a suitably blinded manner, but with the use of a postoperative questionnaire, objectivity could be achieved quite easily and it would be surprising if this were not attempted.

The authors advocate the use of the single breath induction technique with isoflurane for day-case and accident and emergency anaesthesia on the grounds that avoidance of i.v. induction agents will result in rapid recovery. However, the introduction of propofol has reduced the potential benefit to be gained from avoidance of i.v. agents. Unless a clear advantage of inhalation over i.v. induction and maintenance using short acting agents can be demonstrated, the use of the technique would appear to be limited.

M. A. MOORES
Leicester

REFERENCES

1. Lamberty JM, Wilson IH. Single breath induction of anaesthesia with isoflurane. *British Journal of Anaesthesia* 1987; 59: 1214–1218.
2. Loper K, Snook L, Benthuysen J, Bennet H, Reitan J. Rapid anesthetic induction with halothane vs. isoflurane. *Anesthesiology* 1986; **65**: A301.
3. Loper K, Reitan J, Bennet H, Benthuysen J, Snook L. Comparison of halothane and isoflurane for rapid anesthetic induction. *Anesthesia and Analgesia* 1987; **66**: 766–768.
4. Ruffle JM, Latta WB, Snider MT. Single breath halothane oxygen induction in man. *Anesthesiology* 1982; 57: A461.
5. Stevens WC, Dolan WM, Gibbons RT. Minimum alveolar concentrations (MAC) of isoflurane with and without nitrous oxide in patients of varying ages. *Anesthesiology* 1975; 42: 197–200.
6. Ruffle JM, Snider MT. Onset of hypnosis with halothane induction using single breath, triple breath and conventional techniques. *Anesthesiology* 1984; **61**: A498.
7. Wilton NCT, Thomas VL. Single breath induction of anaesthesia using a vital capacity breath of halothane, nitrous oxide and oxygen. *Anaesthesia* 1986; **41**: 472–476.

Sir,—Dr Moores' interest in a single breath induction technique using isoflurane is evident, as he mentions a pilot study carried out in Leicester. We should be interested to see further results of this study and were surprised at Dr Moores' somewhat negative attitude to a technique which his department had thought at one time worth investigating, and which we and others have shown to be acceptable and practical.

Our choice of 2% isoflurane concentration was empirical. Many anaesthetists have noticed that a rapid increase in concentration to a high percentage induces coughing.

We feel that extrapolation from the data of Ruffle and colleagues [1], who used a different anaesthetic, is questionable.

We did not measure induction times because similar studies [1, 2] had difficulties in obtaining useful data. For example, the loss of eyelash reflex is measurable, but not a great deal of use, as it does not coincide with any degree of surgical anaesthesia. Dr Moores says that his department's pilot study recorded a mean induction time of 80 s, but the time when surgery can commence is certainly not 80 s after a single breath induction. Indeed, Ruffle and colleagues [1] stated that spontaneous ventilation of 3.4% halothane for 3–5 min is necessary to produce a surgical plane of anaesthesia.

It is not possible to compare our study with that of Loper and colleagues [3], who used a large induction dose of fentanyl. We conducted our anaesthesia with a conventional multibreath gaseous induction and indicated to the surgeon when the patient was adequately anaesthetized.

Dr Moores is correct, in that a blinded postoperative questionnaire would have been valid, but the initial disparity between the results of the two questions we asked was so large that we continued the initial approach.

Dr Moores has misunderstood our intentions. We were not aiming to displace propofol or other i.v. agents. As stated in our discussion, the single breath induction technique is acceptable to patients; it is possible to use isoflurane or halothane, and for certain procedures the technique offers an alternative to i.v. induction, but there will always be some instances when the i.v. route is not indicated for medical or patient reasons.

J. M. LAMBERTY
Bristol
I. H. WILSON
Zambia

REFERENCES

1. Ruffle JM, Latta WB, Snider MT. Single breath halothane oxygen induction in man. *Anesthesiology* 1982; 57: A461.
2. Wilton NCT, Thomas VL. Single breath induction of anaesthesia using a vital capacity breath of halothane, nitrous oxide and oxygen. *Anaesthesia* 1986; **41**: 472–476.
3. Loper K, Snook L, Benthuysen J, Bennet H, Reitan J. Rapid anesthetic induction with halothane vs. isoflurane. *Anesthesiology* 1986; **65**: A301.

USE OF THE POST-TETANIC TRAIN-OF-FOUR FOR EVALUATION OF INTENSE NEUROMUSCULAR BLOCKADE WITH ATRACURIUM

Sir,—Recently, *British Journal of Anaesthesia* carried two articles on monitoring intense neuromuscular blockade by means of post-tetanic count [1, 2]. As a clinical routine in our department, we use another simple method: the post-tetanic train-of-four. In order to document the need for incremental doses of atracurium to maintain intense blockade, we undertook a simple clinical trial to establish the temporal relationship between the occurrence of twitches in the post-tetanic train-of-four and the first twitch in the pretetanic train-of-four.

The study included 30 ASA grade I–III patients (17 male) aged 16–83 yr. After midazolam 7.5–15 mg by mouth 1 h before surgery, anaesthesia was induced with fentanyl 0.1 mg, thiopentone 4–5 mg kg^{-1} (three patients with etomidate 0.3 mg kg^{-1}) followed by atracurium 0.6 mg kg^{-1} (5 mg given as a priming dose).

To monitor neuromuscular blockade, the ulnar nerve was stimulated transcutaneously at the wrist with supramaximal rectangular stimuli using a peripheral nerve stimulator (NS-3A, Professional Instruments). The trachea was intubated when the response to single twitches (1 Hz) had disappeared completely. To maintain anaesthesia, we used 60% nitrous oxide and 0.8% enflurane in oxygen, with fentanyl 0.1 mg i.v. as necessary. The following mode of stimulation was used every 5 min [3]: train-of-four, tetanus (5 s, 50 Hz) and again train-of-four. We counted the twitch responses of the adductor pollicis muscle felt at the thumb [4].

The response to stimulation was abolished completely in all patients after atracurium 0.6 mg kg^{-1} and recovery began after 15–55 min. In 26 of the 30 patients the first sign was the appearance of twitches in the post-tetanic train-of-four. Fourteen patients needed another 5 min, and none more than 15 min until the first twitch in the pretetanic train-of-four could be felt (fig. 1).

We conclude that the post-tetanic train-of-four is suitable for monitoring intense neuromuscular blockade with atracurium. After the occurrence of any twitch response in the post-tetanic train-of-four, it is necessary to give another bolus of atracurium. Only in this way is it possible to maintain an intense neuromuscular blockade.

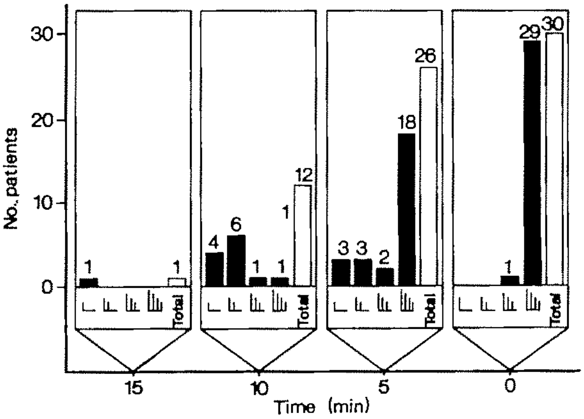


FIG. 1. Numbers of patients who showed twitch responses in the post-tetanic train-of-four 15, 10 and 5 min before, and at the time of appearance of the first twitch in the pretetanic train-of-four.

M. SALATHÉ
M. JÖHR
Lucerne

REFERENCES

1. Bonsu AK, Viby-Mogensen J, Fernando PUE, Muchhal K, Tamilarasan A, Lambourne A. Relationship of post-tetanic count and train-of-four response during intense neuromuscular blockade caused by atracurium. *British Journal of Anaesthesia* 1987; 59: 1089–1092.
2. Ridley SA, Hatch DJ. Post-tetanic count and profound neuromuscular blockade with atracurium infusion in paediatric patients. *British Journal of Anaesthesia* 1988; 60: 31–35.
3. Lee C, Katz RL. Neuromuscular pharmacology. *British Journal of Anaesthesia* 1980; 52: 173–188.
4. Howardy-Hansen P, Viby-Mogensen J, Gottschau A, Skovgaard LT, Chraemmer-Jorgensen B, Engbaek J. Tactile evaluation of the post-tetanic count. *Anesthesiology* 1984; 60: 372–374.

HALOTHANE

Sir,—Professor Spence's letter [1] in response to mine indicates that he has not appreciated the content of the CSM's *Current Problems* (No. 18, September 1986) on halothane. He states that the references quoted in my letter [3, 4] do not support the CSM's recommendations. Yet the excerpts that he has taken from these papers closely mirror statements made in the *Current Problems* article. I quote from the latter: "severe hepatotoxicity can follow halothane anaesthesia; this occurs more frequently after repeated exposures to halothane and has a high mortality. The risk of severe hepatotoxicity appears to be increased by repeated exposures within a short time interval, although even after a long interval between exposures (several years in some patients), susceptible patients have been reported to have developed jaundice. Unfortunately, there is no reliable way of identifying susceptible patients". In addition the CSM's recommendations relating to the importance of taking an anaesthetic history, and contraindication of halothane in patients who have had a history of unexplained jaundice following previous halothane exposure, are identical to the conclusions of Stock and Strunin [3].

The CSM's recommendation: "repeated exposure to halothane within a period of at least three months should be avoided unless there are overriding clinical circumstances", is based on published data and data available to the CSM from yellow card reports which indicate that the majority of cases of severe irreversible liver damage occur when re-exposure to halothane is within this period of time. The recommended interval between exposures is bound to be arbitrary, in that it is reached by balancing the risks of developing hepatotoxicity against the benefits of halothane anaesthesia. The alternative approach, to avoid any further cases of halothane associated hepatotoxicity, would of course be to abandon halothane. The Committee felt this would not be appropriate.

Professor Spence is sadly mistaken in his belief that the CSM did not consult with the specialty of Anaesthesia. The Committee sought the comments and advice of both the

Faculty and the Association of Anaesthetists before its public statement on halothane. In addition, a member of the Board of the Faculty of Anaesthetists was a member of the CSM at the time the CSM made its recommendations on halothane.

A. W. ASSCHER
London

REFERENCES

1. Spence, AA. Halothane. *British Journal of Anaesthesia* 1988; **60**: 479–480.
2. Asscher AW. Halothane. *British Journal of Anaesthesia* 1988; **60**: 479.
3. Stock JG, Strunin L. Unexplained hepatitis following halothane. *Anesthesiology* 1985; **63**: 424–439.
4. Neuberger J, Williams R. Halothane anaesthesia and liver damage. *British Medical Journal* 1985; **289**: 1136–1139.

Sir,—The statements quoted by Professor Asscher in his first paragraph are not disputed by me and have formed the basis of practice by most anaesthetists for some years. My main concern is that the CSM has changed the "recommended interval" from 28 days to 3 months. They have also stated that "unexplained ... pyrexia in a patient following exposure to halothane is an absolute contraindication ...". To most doctors these pronouncements would signify either that halothane is more dangerous than had been supposed previously, or that new information had arrived to allow better definition of the interval. Professor Asscher says that the recommended interval is bound to be arbitrary and implies that it was reached by balancing the risks. As there is no inhalation agent (except chloroform) which offers the potency of halothane, it would be of interest to know the factors used in the balance.

I believe that the CSM could have been in no doubt that their statement would cause a substantial shift away from halothane in practice, while providing an invaluable resource for anyone seeking litigation against an anaesthetist unfortunate enough to have a patient who developed hepatocellular injury associated with (not necessarily caused by) repeat halothane anaesthesia. In these circumstances, precision—including control of other factors associated with postoperative hepatitis—would have been much superior to guesswork.

On the matter of the CSM's consultation with the specialty, I have perused correspondence filed at the Association of Anaesthetists and at the Faculty of Anaesthetists. The Board of Faculty (of which I am a member) was asked, in April 1986, if the increased interval would have an impact on practice. We said it would and a wish was expressed to view the data held by the CSM. The Board was given to understand, on good authority, that discussion of the interval was not open to us; the decision had been made. The CSM's letter of March 20, 1986 to both Association and Faculty, which I had not seen previously, seems to me to call for a meeting with your senior medical officer. Surprisingly, no meeting was ever arranged. On the contrary, the clear impression of the Board of Faculty was that our response was sought only in respect of the narrow question given above. I remember widespread indignation at this position. I understand from members of Council of the Association that they considered themselves to be in a similar position. In any case, no effective consultation ever took place. Thus the CSM went into print without the advice (particularly on medico-legal implications) which they initially set out to obtain. I accept that there may have been genuine misunderstanding between the bodies concerned, but that is no justification of substantial undermining of a drug which has been the most important development in anaesthesia since the 1950s.

It is not my intention to play the role of Canute. My anxiety about the current position of halothane, in the light of the September 1986 statement, is widely shared both in Britain and abroad. My concern is heightened by the thought that—notwithstanding the intentions of all those concerned—the consultation that was clearly hoped for on all sides did not take place to an adequate degree. In the circumstances, Professor Asscher (who was not Chairman of the CSM at the time) must see the case for reconsidering the advice on halothane. I hope he will.

A. A. SPENCE
Edinburgh

Br. J. Anaesth. (1988), **61**, 125–127

BOOK REVIEWS

Problems and Advances in Respiratory Therapy. International Anesthesiology Clinics. By G. Racz. Published by Little, Brown and Co., Boston. Indexed; illustrated.

This edition of *International Anesthesiology Clinics* achieves its objective in providing succinct reviews of 13 aspects of the respiratory system, relevant to the clinical anaesthetist. There are three main areas of interest: respiratory physiology and pathophysiology, respiratory problems in different clinical settings, and equipment used in clinical practice.

The book is written by one French and 17 American authors. It opens with reviews of the physiology of oxygenation and oxygen transfer and acid–base balance. The pathophysiology of the hyper-reactive airway, acid aspiration and the respiratory effects of malnutrition are then discussed. Further chapters examine the haemodynamic effects of pulmonary insufficiency and the injuries sustained by the respiratory mucosa during artificial ventilation of the lungs. The clinical management of respiratory problems is considered for children with upper airway obstruction and patients undergoing neurosurgery, cardiovascular surgery and surgery for morbid obesity. Lastly, there is an account of equipment used for the monitoring of respiratory function in clinical practice and in high frequency ventilation of the lungs.

No attempt at a comprehensive review of the respiratory system is made. The chapters are quite different. Each is concise and readable and restricted well to the subject considered. They vary from giving original data or detailed reviews of individual studies, to the opinions of an author on his subject. Each chapter contains detail and explanation in digestible proportions. The opening chapters on the physiology of oxygen transport and acid–base balance are as lucid as any others that have attempted to summarize these fundamental aspects of respiratory physiology.

There is some repetition of the mode of action of respiratory drugs and the pharmacology is understandably American. Apart from this, the volume translates well for practice in the United Kingdom.

References vary from none to 60 for each chapter and date from 1896 to 1984. The book is illustrated with 72 figures and 10 tables. The line diagrams and photomicrographs are more successful than the printed photographs.

This volume is a worth-while read and could well be used to encourage a librarian to stock the series.

D. Duthie

Radiology for Anesthesia and Critical Care. Edited by C. H. Murphy and M. R. Murphy. Published by Churchill Livingstone. Pp. 273; indexed; illustrated. Price £37.50.

This American text, edited by a radiologist and an anaesthetist, is intended to help the practising clinician understand common radiological investigations. The major emphasis is therefore placed on the interpretation of chest x-rays. The first chapter is entitled "Understanding the Image", and it provides an excellent introduction to the principles of thoracic radiology and common pitfalls in interpretation. The second chapter, "Preoperative Evaluation", discusses the value of the routine chest x-ray and has a number of well-chosen illustrations of pulmonary and cardiac disease, but fails to mention radiology of the upper airway or of the cervical spine; this is a surprising omission.

Subsequent chapters are devoted to pulmonary shadowing, the adult respiratory distress syndrome (ARDS), thoracic trauma, radiology of the abdomen, monitoring and life-support devices, and special imaging modalities (CT, NMR and radioisotope scans). There are four excellent chapters on paediatric radiology, including cardiac disease and airway pathologies; the book concludes with general considerations of anaesthesia for radiological procedures, and a discussion of radiation safety. The chapter on ARDS omits to mention miliary tuberculosis as a cause for the syndrome and does not reference the use of pulmonary wedge angiography in the assessment of severity of ARDS. The anatomy of the paediatric airway is described adequately, but not that of the adult; this would have been helpful. Head and neck injuries are not discussed.

The quality of the illustrations is excellent, particularly considering the nature of so many portable x-rays of critically ill patients. The text is written in American English, and on the whole the quality of writing is good. The references are adequate, the index accurate, and the book is well-directed towards its intended market. At £37.50 I would recommend it to all intensive care units; it will be consulted frequently by those involved in intensive care and those involved in perioperative care, by candidates for the FFARCS examination, and by those involved in teaching.

J. F. Bion

Closed-Circuit System and Other Innovations in Anaesthesia. Edited by R. Droh and R. Spintge. Published (1986) by Springer Verlag, Berlin. Pp. 252; indexed; illustrated. Price £36.25.

This book provides a report on papers presented at an international meeting in Lüdenscheid, May 1984, for discussion on "Innovations in Management, Technology and Pharmacology". There are four sections containing papers on, respectively, the functioning and use of closed circuit and low-flow anaesthetic breathing systems; non-invasive monitoring techniques; applied cardiovascular and respiratory physiology; and pharmacology and therapeutics. There is much variety in the format of individual chapters, so that some contributions provide detailed accounts of particular fields of study whilst others provide only brief and relatively uninformative abstracts.

The section on closed circuit and low-flow breathing systems occupies 110 of the 252 pages of the book and provides descriptions ranging from practical use for anaesthesia in particular surgical fields to specific details of the behaviour and the means for monitoring the behaviour of these systems. There are some editorial surprises here: a chapter entitled "Closed-circuit anaesthesia for cardiac patients" makes practically no reference to "cardiac patients" and it is unclear why three chapters by the same author frequently repeat illustrations.

The section on monitoring includes chapters principally on non-invasive measurement of tissue gas tensions, arterial pressure and other indices of cardiovascular function. The section on applied physiology has chapters describing different techniques for the management of artificial ventilation during severe respiratory failure, oxygenation within the myocardium, autotransfusion, transfusion with stroma-free haemoglobin solutions and mechanics within the peripheral circulation. This is followed by a final section of three chapters on the relationship between variability in pharmacological responses and diurnal physiological changes (Chronopharmacology) and the use of either intrathecal or extradural opioids.

As this book is a report from an international meeting, with disparity of individual contributions with respect to both subject matter and depth of treatment, it is unlikely that many individuals will wish to purchase a copy. However, those who do gain access to the book are likely to find at least a few chapters of considerable interest.

D. Wetherill

The I.C.U.—A Cost Benefit Analysis. (Excerpta Medica International Congress Series 709.) By D. R. Miranda and D. Langrehr. Published by Elsevier Science Publishers BV. Pp. 236; indexed. Price US $72.00.

This is the report of the proceedings of a Symposium held in Gröningen in February 1986. Many of the best known figures in intensive therapy contributed. The objectives of the meeting were to consider the economic problems created by intensive therapy and try to balance these against the moral issues. Each speaker emphasized the difficulty of satisfying these conditions.

As stated, the problems are: (1) the cost of intensive therapy is open-ended and increasing; (2) the return on the investment in terms of quality of added life years (referred to as QUALYs by several speakers) was particularly questionable because it is apparent that the greatest expense is generated by those patients with the poorest prognosis.

Although the problem cannot be ignored anywhere, it is more acute in those societies in which the patient, his immediated family or commercial insurance companies are responsible for the bill.

The introductory chapter by Professor Ian Ledingham sets out the problem and some of the options very clearly. This is followed by an evaluation of the economic consequences of high technology medicine. Other chapters demonstrated the differences which exist between countries in their practice of intensive care. Each chapter is interesting and repays study, although some were less directly relevant than others. To the reviewer, one of the best was from the Department of, Psychology at the University of Gröningen. This describes a model for resolving such problems, although the author made no attempt to lay down criteria for selection which, as he stated, must ultimately depend upon the evaluation of human life and the reliability of survival statistics. He also pointed out that such calculations take no account of the effects of continuously improving methods of treatment. All of the right questions are asked, but the answers cannot be based only upon economic considerations.

Anyone who is seriously concerned with the costs of health care would benefit from reading this book and as such it can be recommended.

Presumably because of the way in which the data were collected and the haste of the publication, there are numerous misprints and in some cases the English translation is stilted.

J. C. Stoddart

Geriatric Anaesthesia. Principles and Practice. Edited by C. R. Stephen and R. A. E. Assaf. Published (1986) by Butterworths Publishers, Boston. Pp. 384; indexed. Price £39.50.

Much has already been written about the ageing process and associated disease states which affect the elderly, and not only in anaesthetic journals and textbooks. This text, with 22 contributing authors, devotes the first 155 pages to reviewing the physiology of the elderly. The section on drug interactions is disappointing, consisting of four pages of text and six tables, and the chapter on evaluation and premedication is light on clinical recommendations such as communication problems which may arise, and does not comment on evaluation of pacemaker function. It does, however, advocate that small doses of droperidol induce, in most patients, a tranquil state of disassociation that obviates the fear and apprehension of the immediate environment—a remark which is inconsistent with the views of many British anaesthetists.

Naturally, with a plethora of authors, repetition is difficult to avoid. There are three chapters on the cardiovascular system: the chapter on the effects of anaesthetics is a good review but, in the section which discusses anaesthesia and the hypertensive patient, withdrawn drugs such as Althesin are still advocated.

A superficial approach is made to the advantages and disadvantages of regional anaesthesia; the eternal extradural *v.* spinal debate is ignored and the postoperative benefits or otherwise of these techniques are not discussed.

Monitoring the patient in the operating room does have a small section on monitors and cardiac indications for pacing therapy and a paragraph on anaesthetic management for insertion of pacemakers. Slanted towards major surgery, this chapter emphasizes the importance of invasive monitoring.

The section on fluid management provides some useful information on perioperative procedures, but the postoperative management of patients, a hazardous time, is not discussed anywhere else in the book, which concludes with a disappointing epidemiological study on risk factors and outcomes.

The tables are clear, although one (Table 1.2) has no legend. The index is acceptable. A useful list of references is appended to each chapter. This reviewer may be seen to be disappointed with this book, and can find little basis for recommending it to anaesthetists.

J. Lumley

Anaphylactic Reactions in Anesthesia and Intensive Care. By J. H. Levy. Published by Butterworths. Pp. 173; indexed: illustrated.

Over the past 10 years, the increasing interest in anaphylactoid or hypersensitivity reactions has been characterized by a stream of articles and books. Curiously, the majority of these have come from the U.K. and Australasia, with considerable interest also in France and Germany. It is hard to believe that the frequency of reactions is so regionalized and, presumably, the distribution of publications depends mainly on the interest of the authors. This is the first book from the U.S.A. on the subject, and benefits from having a single author and a strong clinical basis.

Anaphylactic reactions are defined at the outset as involving an antigen–antibody interaction and are reproducible on challenge with a specific antigen. However, the book also discusses the much wider field of all histaminoid reactions which resemble the purely immunological phenomenon. The first part is devoted to mechanisms and classifies immune-based reactions into the traditional four types, of which only Type I is of interest to anaesthetists.

The clinical description of the reactions covers the well-known signs affecting the cutaneous, cardiovascular, respiratory and gastrointestinal system. This is well supported by the author's detailed cardiovascular study of eight reactions to a variety of stimuli, although it is perhaps surprising that there was no tachycardia in most of the reactions studied. Dr Levy also points out the unreliability of cutaneous manifestations as diagnostic features and reminds us that in bee stings the highest observed histamine concentrations were associated with hypotension and not cutaneous manifestation. However, it may be said that, in most reactions at the induction of anaesthesia, erythema and tachycardia have been reported. These differences only serve to emphasize the diversity of both causative factors and clinical manifestations.

The causative agents of anaphylactoid reactions are discussed at length and, interestingly, local anaesthetic agents receive as much attention as the induction agents, while neuromuscular blocking drugs receive more. This arises from the fact that drugs in the Cremophor vehicle were never in regular use in the U.S.A. and from the greater use of local anaesthetic techniques. The author does, however, stress that hypersensitivity reactions to the administration of local anaesthetics are rare and are usually a result of the presence of other substances. A variety of other substances used by anaesthetists which may cause collapse is discussed, including chymopapain and protamine.

The preoperative investigation and management of patients receives a detailed chapter with a full description of methods of skin testing. This is followed by a chapter on differential diagnosis with overdosage and many spontaneous mishaps may be confused with anaphylactoid reactions. The book ends with four chapters giving detailed regimens for treatment and some individual case reports. There is certainly some repetition in these chapters, but the book is intended both as a review of the problems and as a guide to urgent treatment. There is sound practical advice here, based on the author's experience and reading.

This is a book which should be in the library of all Anaesthetic Departments interested in the problem of anaphylaxis, for there is much information which is not available in other textbooks.

R. S. J. Clarke

Papers for publication and all editorial communications should be addressed to the Editor, University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW; business communications to the publishers: Professional & Scientific Publications Ltd, BMA House, Tavistock Square, London WC1H 9JR.

The GUIDE TO CONTRIBUTORS can be found on pages viii, x & xii of the advertisement section of this issue.

Published monthly: Annual subscriptions: UK/Eire £54.00; Abroad £85.00; USA $117.00 (direct orders only). Trainee rate UK/Eire £33.00; Abroad £50.00. Airmail rates on application. ISSN 0007–0912. Orders must be accompanied by payment; cheques should be made payable to Professional and Scientific Publications. Orders and payments should be sent to Professional and Scientific Publications, BMA House, Tavistock Square, London, WC1H 9JR. Orders in the United States of America may be sent to Professional and Scientific Publications, Box 560B, Kennebunkport, Maine 04046.

Group Advertisement Manager, Mr R. Hayzen.
Advertisement Manager, Mrs S. Rowe
BMA House, Tavistock Square, London WC1H 9JR. 01-387 4499.

Whilst every effort is made by the publishers and editorial committee to see that no inaccurate or misleading data, opinion or statement appears in this Journal, they wish to make it clear that the data and opinions appearing in the articles and advertisements herein are the responsibility of the contributor or advertiser concerned. Accordingly, the publishers and the editorial committee and their respective employees, officers and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinion or statement. Whilst every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described within this Journal, should only be followed in conjunction with the drug manufacturer's own published literature

---

© Copyright: 1988 British Journal of Anaesthesia
All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the *British Journal of Anaesthesia*.

Published by Professional and Scientific Publications.
Printed in Great Britain by the University Press, Cambridge

Anaesthesia and Intensive Care

Journal of the Australian Society of Anaesthetists

Published quarterly
Overseas Subscription Rates for 1988: Aust $60.00 per year (*surface mail*)
Aust $60.00 equals approximately **US $42.00** or **UK £24.00** (*January 1988*)

SUBSCRIPTION FORM

I wish to subscribe to **ANAESTHESIA AND INTENSIVE CARE** commencing with the current volume.

NAME . . . .
(BLOCK LETTERS PLEASE)

ADDRESS . . . .

. . . . POSTCODE. . . . .

COUNTRY . . . . DATE. . . . .

☐ (✓) PLEASE SEND BY SURFACE MAIL

☐ (✓) MY PAYMENT IS ENCLOSED

☐ (✓) PLEASE SEND ME INFORMATION ON AIR MAIL RATES FOR MY REGION

☐ (✓) PLEASE INVOICE ME WITH THE FIRST ISSUE

Annual Subscription Rates (1988 rates):

★ **Within Australia**	— **surface mail**	: **Aust $45.00**	*back issues: $11.00*
	— air mail	: Aust $55.00	*back issues: $14.00*
★ **Outside Australia**	— **surface mail**	: **Aust $60.00**	*back issues: $15.00*
	— air mail	: Rates available on request	

Aust $60.00 equals approximately **US $42.00** or **UK £24.00** (January 1988)

Please mail to: **Subscription Department**
ANAESTHESIA AND INTENSIVE CARE
PO Box 600
EDGECLIFF, NSW 2027
AUSTRALIA

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 61, No. 1 *Published monthly* JULY 1988

Annual subscriptions (post free): U.K./Eire £54.00; Abroad £85.00; USA $117.00 (Direct orders only); Trainee rate: U.K./Eire £33.00; Abroad £50.00; Airmail rates on application ISSN 0007–0912

Subscription Department, Professional and Scientific Publications, BMA House, Tavistock Square, London, WC1H 9JR, England

---

CONTENTS

PAGE

EDITORIAL: Anaesthesia and myocardial ischaema . 1
G. Smith

SYMPOSIUM ON ANAESTHESIA AND MYOCARDIAL ISCHAEMIA

Aetiology of ischaemic heart disease................ 3
D. A. Wood

Myocardial ischaemia: progress in drug therapy.... 11
D. B. Barnett

Perioperative myocardial infarction 24
R. Haagensen and P. A. Steen

Assessment of the patient with known or suspected ischaemic heart disease for non-cardiac surgery .. 38
L. Goldman

Experimental models of myocardial ischaemia...... 44
P. Foëx

Anaesthesia and ischaemic heart disease: laboratory results 56
D. Kettler and A. Hoeft

Myocardial ischaemia associated with general anaesthesia. *A Review of Clinical Studies*........ 68
S. Reiz

Anaesthetic considerations for the patient with coronary artery disease 85
C. Prys-Roberts

Anaesthesia for coronary artery bypass graft 97
J. B. Streisand and K. C. Wong

PAGE

ABSTRACTS

Proceedings of the Anaesthetic Research Society, Liverpool Meeting, March 25–26, 1988.......... 105P

CORRESPONDENCE

Blocked ear after extradural injection—a clarification 119
Routine use of atropine in obstetric anaesthesia 119
Hepatotoxicity after general anaesthesia 120
Potential problems of using both opioids and local anaesthetic 121
Single breath induction of anaesthesia with isoflurane 121
Use of the post-tetanic train-of-four for evaluation of intense neuromuscular blockade with atracurium. 123
Halothane 123

BOOK REVIEWS

Problems and Advances in Respiratory Therapy. International Anesthesiology Clinics............... 125
Radiology for Anesthesia and Critical Care......... 125
Closed-Circuit System and Other Innovations in Anaesthesia.. 125
The I.C.U.—A Cost Benefit Analysis................ 126
Geriatric Anaesthesia. Principles and Practice 126
Anaphylactic Reactions in Anesthesia and Intensive Care 126

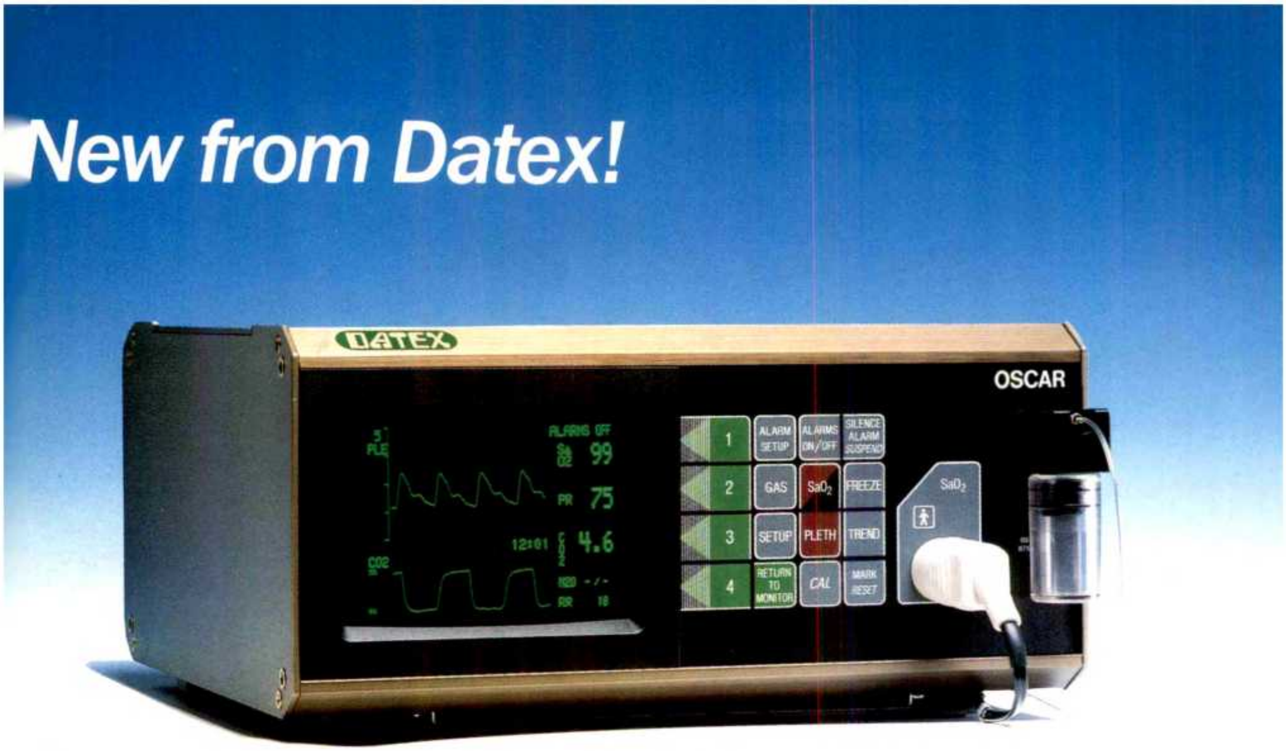
Rec.
19.10.88

VOLUME 61 • NUMBER 2 • AUGUST 1988

British Journal of Anaesthesia

LIBRARY

Editor: GRAHAM SMITH



New from Datex!

Add our new Oscar™ integrated CO_2 and SaO_2 monitor – and your ECG no longer has to stand alone

There is growing acceptance by anesthesiologists that both pulse oximetry and CO_2 monitoring are of invaluable help in the timely detection of anesthesia incidents. Our new Oscar™ CO_2 and SaO_2 monitor allows you to meet these emerging standards of care with one instrument.

Oscar™ is a compact, rugged monitor which fully meets the requirements of the operating theater. The sharp, bright video screen clearly displays the vital data and maximizes the diagnostic value of the capnogram and the plethysmographic pulse waveform.

Continuously monitoring ventilation and tissue oxygenation, Oscar™ effectively complements your clinical eye. And you can rely on Oscar™ to perform to expectation, since it combines Datex's proven CO_2 sensor technology with versatile pulse oximetry.

Oscar™ is the latest addition to Datex's line of anesthesia monitors, the most comprehensive range available.

To see how well Oscar™ can meet your need for additional vigilance from capnometry and pulse oximetry, please contact your local Datex distributor or contact us direct:

In the U.K. please contact
Vickers Medical, tel. 0256 29141
or telex 858697

DATEX

Datex/Instrumentarium Corp.
P.O.Box 357
SF-00101 Helsinki Finland
Tel. +358 0 394 11 Telex 126252

"I would have everie man write what he knowes and no more."—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 61, No. 2 AUGUST 1988

EDITORIAL

TEST DOSES IN EXTRADURAL BLOCK

It has long been common practice to inject a test dose of local anaesthetic when performing extradural block. This is undertaken in order to determine if the needle or the catheter tip is inadvertently within either the subarachnoid space or an extradural vein. A few millilitres of local anaesthetic injected into the subarachnoid space produces an obvious spinal anaesthetic after some minutes. An i.v. injection can be diagnosed if adrenaline is added to the test dose in sufficient quantity to cause a marked but short-lived tachycardia. All seems logical and clear, yet several doubts still remain as to the efficacy of test doses. Many anaesthetists do not use them unless they have serious doubts on the correct position of the needle or catheter. Moreover, in the great majority of reported cases of high/total spinal anaesthesia, or serious systemic toxicity, during attempted extradural block, a test dose was used. False negative tests are dangerous. False positives are a considerable nuisance, as the procedure must be repeated when in fact there is no incorrect placement.

False negative test doses for intrathecal placement are a result of an inadequate dose being used, an insufficient time being allowed for a spinal anaesthetic to develop, or inadequate testing for a spinal anaesthetic. Thus to inject 2 ml of 0.25 % bupivacaine, wait 2–3 min and then ask the patient to move the feet or toes will give a negative result more often than a positive one if the drug has indeed been injected into the subarachnoid space. Such a small amount of bupivacaine will not cause motor paralysis for several minutes, if at all. The patient must be asked about subjective sensations in the lower limbs such as warmth, tingling or numbness, and if necessary testing with pinprick or cold sensation should be carried out. A larger dose, 4–5 ml, is likely to produce a more rapid and clearly defined response, without danger of an unduly high spinal blockade. However, the ordinary solutions of bupivacaine (being isobaric or slightly hypobaric) are slow to act compared with hyperbaric solutions and there is logic in using such a solution, say 1.5–2 ml of 5 % lignocaine, which will give an obvious spinal block in 2–3 min, especially in the dependent limb of the patient in the lateral position.

Subdural injections of local anaesthetic are notoriously difficult to diagnose because, although they cause widespread blockade, this is often slow in onset. The use of high concentration–small volume test doses could make the diagnosis easier.

For determining i.v. placement, the situation is more complicated, as most test doses, even 4 ml of 0.5 % bupivacaine, produce only minimal subjective symptoms in the patient. This has led to the inclusion of adrenaline in the test dose and it has been shown that even small quantities, for example 4 ml of 1 in 200 000 (20 μg) adrenaline will cause an increase in heart rate of 20–40 beat min^{-1}. However, the detection of this evanescent effect requires continuous monitoring of the heart rate (using an ECG and not a finger on the pulse). In some nervous subjects, it is difficult to get a stable rate before injection, and increases of 20 beat min^{-1} commonly occur spontaneously. Unpremedicated mothers about to undergo Caesarean section are not among the calmest of patients, and are already under the influence of endogenous adrenaline. Increasing the dose to, say, 40–50 μg would make detection of i.v. placement easier.

An important confounding factor in this whole problem relates to extradural catheter design and the use of multiple holes. It is easily demonstrated that a low pressure, slow injection causes the injectate to escape from the proximal hole, while a high pressure, fast injection causes it to escape from the distal hole. As the holes are nearly 1 cm apart on some catheters, it is possible to have the distal hole misplaced, and the proximal one correctly placed within the extradural space. Although single–hole catheters are available, for some reason they are not popular. If multiple holes are preferred, the test dose should be given rapidly.

Probably the most dangerous aspect of a false negative test dose is the confidence it inspires in the anaesthetist that all is well and the main dose can be injected with impunity. Thus very large amounts are given before it is obvious that the drug has been administered i.v., and may considerably exceed the convulsant dose and cause cardiovascular collapse. As noted in the accompanying paper, it is the rate of increase of brain concentration of local anaesthetic, rather than a defined plasma concentration which causes CNS symptoms [1].

The anaesthetist must have a high degree of suspicion that, in spite of a negative result, misplacement can still be present. Paradoxically, if a test does is *not* used, it is much easier to entertain this suspicion and to be much more cautious when injecting the main dose. To avoid disasters the following should be adhered to:

(1) After insertion of the needle or catheter, *gently* aspirate and observe any fluid leaving the extradural space.

(2) If a test dose is used, inject sufficient drug (with added adrenaline) rapidly and wait long enough to detect any effect. During the first 90 s, observe the heart rate continuously and do not accept the absence of spinal anaesthesia in less than 5 min. Question the patient for subjective effects.

(3) Even if the test is negative, the main dose must be injected *slowly*, for example, not faster than 10 ml min^{-1} or in 5-ml aliquots every 60–120 s. Talk to the patient throughout the injection and ask for the early symptoms of toxicity, such as numbness of the mouth, tinnitus, etc. Beware of the patient who talks or behaves strangely.

(4) Be prepared to deal expeditiously (and successfully) with either systemic toxicity or a high/total spinal block. The procedure for these should be laid down in each unit and well known to junior staff performing extradural blockade.

D. B. Scott

REFERENCE

1. Haasio J, Hekali, R, Rosenberg, PH. Influence of premedication on lignocaine-induced acute toxicity and plasma concentrations of lignocaine. *British Journal of Anaesthesia* 1988; **61**: 129–132.

Br. J. Anaesth. (1988), **61**, 131–134

INFLUENCE OF PREMEDICATION ON LIGNOCAINE-INDUCED ACUTE TOXICITY AND PLASMA CONCENTRATIONS OF LIGNOCAINE

J. HAASIO, R. HEKALI AND P. H. ROSENBERG

SUMMARY

The effects were studied, in eight healthy volunteers, of premedication with diazepam 0.14 mg kg^{-1} by mouth or hyoscine 6 μg kg^{-1} + morphine 0.2 mg kg^{-1} i.m., or no premedication, on toxic symptoms and plasma concentrations after rapid i.v. injection of lignocaine 1 mg kg^{-1}. The α_1-acid glycoprotein (AAG) and albumin plasma protein fractions were assessed. A variety of mild central nervous system (CNS) symptoms were experienced after the bolus of lignocaine. However, there was no correlation between premedication and degree of severity or number of CNS symptoms. The highest single arterial plasma concentration of lignocaine was 11.0 μg ml^{-1}, 1 min after injection. There was no correlation between plasma concentration of lignocaine and occurrence of CNS symptoms. Furthermore, there was no correlation between AAG or albumin plasma concentrations and lignocaine plasma concentrations.

Approximately 30% of the total dose of local anaesthetic used for i.v. regional anaesthesia (IVRA) is flushed into the systemic circulation when the tourniquet is released [1], and mild central nervous system (CNS) toxic symptoms often ensue. As a rule, non-protein bound (free) concentrations of drugs in plasma relate more closely to pharmacological and toxic effects than do total (bound plus free) concentrations [2]. Different drugs may influence the degree of protein binding of local anaesthetics and thereby affect the ratio between free and protein bound drug [3, 4]. On the other hand, the degree of CNS depression by a premedicant drug may affect the subjective perception of toxic symptoms.

We have studied the CNS toxic effects of a rapid i.v. injection of lignocaine 1 mg kg^{-1}, and its plasma concentrations, in individuals who had been given diazepam or hyoscine + morphine, or no premedicant drug.

SUBJECTS AND METHODS

Eight healthy anaesthetists (table I) participated in the randomized, cross-over study which had been approved by the Ethics Committee of our institution. None of the subjects had taken any drug known to affect plasma protein binding of local anaesthetic. After fasting for at least 3 h, they were given diazepam 0.14 mg kg^{-1} by mouth or hyoscine hydrobromide + morphine hydrochloride (hyoscine 6 μg kg^{-1} and morphine 0.2 mg kg^{-1}) i.m., or no premedication. For each individual, the interval between experiments was at least 2 days.

The subjects were studied in a supine position; ECG was monitored continuously and systemic arterial pressure was recorded with an automatic oscillotonometer. A cubital vein and the radial artery (in the arm not used for injecting lignocaine) were cannulated for blood sampling. One hour after premedication, a 2% lignocaine solution (preservative-free) was injected rapidly (1 ml s^{-1}) in a dose of 1 mg kg^{-1} (simulating 30% of an IVRA dose or an antiarrhythmic dose of lignocaine) into an antecubital vein. Subjective and objective evidence of toxicity were noted by the subject, the observer (investigator) or both. The degree of severity of the CNS symptoms was rated in the order shown in table II (top to bottom).

This article accompanies the Editorial.

J. HAASIO, M.D.; R. HEKALI, M.SC.; P. H. ROSENBERG, M.D.; Department of Anaesthesia, Surgical Hospital, Helsinki University Central Hospital, SF-00130 Helsinki, Finland.

Accepted for Publication: December 2, 1987.

Correspondence to J.H.

TABLE I. *Subject characteristics*

Subject No.	Age (yr)	Sex (M/F)	Weight (kg)	Height (cm)	AAG (g litre^{-1})	Albumin (g litre^{-1})
1	42	M	83	185	0.55–0.68	43–45
2	33	M	91	190	0,48–0.54	46–48
3	40	M	80	184	0.43–0.48	43–44
4	29	M	60	167	0.39–0.55	49–55
5	34	M	87	181	0.38–0.41	45–54
6	32	M	85	184	0.43–0.51	46–51
7	40	F	48	152	0.21–0.37	41–45
8	31	F	64	166	0.19–0.43	42–48

For determination of free and plasma protein-bound concentrations of lignocaine, arterial (0, 1, 2, 5 and 10 min) and venous (0, 2, 5, 10, 20, 30 and 60 min) blood samples were drawn. The arterial cannula was removed after the last arterial sample. After centrifugation, the plasma was stored at −20 °C until required for analysis. Lignocaine concentrations were determined by gas chromatography [5]. Unbound lignocaine was separated from plasma using an ultrafiltration method (Amicon Micropartition System). The fraction percentages were corrected (mean correction coefficient 1.14) for the deviation in test temperature (25 °C) and sample pH (7.75–7.80) from physiological values.

Alpha$_1$-acid glycoprotein (AAG) concentrations in plasma from a venous sample obtained immediately before premedication were measured by radial immunodiffusion on M-partigen plates [6], and by an immunoturbidometric method (Kone Progress, Espoo, Finland) with antiserum and standards from Orion Diagnostica (Espoo, Finland). Albumin concentrations were estimated by an automatic technique with bromocresol green binding [7].

TABLE II. *Subjective side effects. Dz = Diazepam; H-Mo = hyoscine + morphine*

	Premedication		
	Dz	H-Mo	None
Numbness mouth/tongue	8	5	5
Tingling mouth/tongue	0	1	0
Metallic taste	2	0	2
Dizziness/lightheadedness	4	1	3
Auditory disturbances	5	6	8
Euphoria	0	0	3
Visual disturbances	0	2	2
Slurred speech	2	4	3
Twitching	0	0	1
Totals	21	19	27

Linear regression analysis was used to evaluate the correlation between the data (number of symptoms, lignocaine plasma concentrations, plasma protein concentrations). Both univariate and multivariate repeated measures analyses of variance (SAS 1985) were performed to test the effects of premedication on plasma concentrations of total and free lignocaine, separately for venous and arterial concentrations. A polynomial transformation was used to test for trends in time-dependent measurements. $P < 0.05$ was considered significant. All values are reported as mean ± SEM.

RESULTS

Effect of premedication. The effect of diazepam was described as mildly sedative and generally pleasant. In all subjects hyoscine–morphine clearly caused marked sedation, drowsiness and dry mouth (but no euphoria), which lasted for several hours after the lignocaine test.

CNS symptoms after i.v. lignocaine. A variety of mild CNS symptoms were experienced 24–45 s after the bolus injection of lignocaine (table II). According to the subjects' reports, the symptoms lasted for 5.0 ± 1.4 min with diazepam (in one subject mild symptoms of lightheadedness persisted for up to 14 min), 2.5 ± 0.3 min with hyoscine–morphine and 4.0 ± 0.6 min, on average, with no premedication. Although the subjects premedicated with hyoscine plus morphine were all sedated heavily and frequently had trouble controlling their speech, they nevertheless reported CNS symptoms similar to those reported when diazepam or no premedication were given.

There was no correlation between premedica-

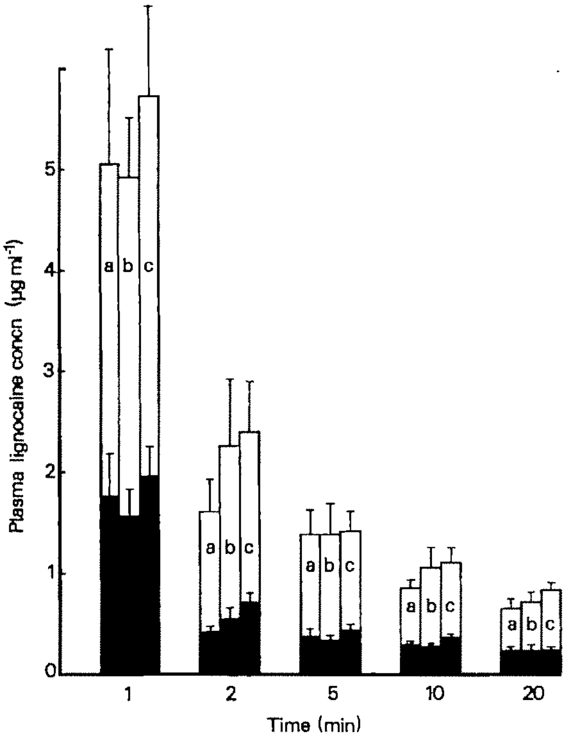


FIG. 1. Plasma concentrations of lignocaine (free and total) (mean ± SEM). a = No premedication; b = diazepam; c = hyoscine + morphine. Black area = free; black + white = total. One-minute sample is arterial, others venous.

tion and degree of severity or number of CNS symptoms.

Plasma concentrations of lignocaine, plasma proteins and toxic symptoms. The mean lignocaine plasma concentrations are shown in figure 1. The highest single arterial plasma concentration was 11.0 µg ml^{-1}, 1 min after injection. The subject with the maximal arterial free lignocaine concentration of 3.3 µg ml^{-1} had symptoms similar to the one with a concentration of 0.8 µg ml^{-1}. There was no correlation between plasma concentrations of lignocaine and occurrence of CNS symptoms. There was no correlation between AAG (0.190–0.680 g litre^{-1}) or albumin (41–55 g litre^{-1}) plasma concentrations (table I) and the total or free fraction (percentage) of lignocaine.

ECG was normal and systemic arterial pressure remained stable throughout each experiment.

DISCUSSION

Our results indicate that pretreatment with diazepam or with hyoscine + morphine does not influence acutely induced symptoms of lignocaine toxicity to any measurable extent. Interestingly, despite relatively heavy sedation with hyoscine and morphine, the subjects perceived toxic symptoms surprisingly well. Although anxiety may promote the production of CNS symptoms by local anaesthetics [8], light or heavy sedation in the participating professional volunteers did not significantly affect the symptoms. Therefore, it may be anticipated that the quality of possible toxic CNS symptoms, for example after an inadvertent intravascular injection in connection with an extradural test dose, is not affected by premedication.

The binding of lignocaine to plasma proteins seems to have little effect on first pass uptake of lignocaine by brain tissue [2], indicating rapid dissociation of the drug–protein complex during the first transit through the organs.

As a basic drug, lignocaine is bound primarily to the AAG fraction of plasma proteins [9]. Although a small part of the diazepam in the circulation is bound by AAG [9], albumin is the major binding protein for diazepam, and for the alkaloid morphine [3, 10]. Thus significant exclusion of lignocaine from high-affinity plasma protein binding sites by diazepam or morphine should not be expected. When lignocaine is administered in therapeutic antiarrhythmic doses, approximately 23 % of protein binding in plasma is to albumin [11]. However, albumin has a high binding capacity, and different drugs appear to have different binding sites [3, 12]. In healthy subjects with normal concentrations of albumin, therefore, any measurable pharmacokinetic interaction achieved with relatively modest (albeit therapeutic) concentrations of diazepam or morphine may not occur. The plasma protein fraction which binds hyoscine does not seem to be known. Because of the relatively small dose of hyoscine, a possible protein-binding interaction with lignocaine does not need to be considered.

The lack of correlation between plasma concentrations of lignocaine and toxic symptoms supports the concept that it is the rapidity of exposure of brain cells to local anaesthetics, rather than a defined concentration in blood, that causes CNS symptoms [2, 13].

ACKNOWLEDGEMENTS

We wish to thank Ms Aira Alila for the gas-chromatographic determinations of the lignocaine concentrations.

This study was supported by a grant from the Sigrid Juselius Foundation (P.H.R.), which is gratefully acknowledged.

REFERENCES

1. Tucker GT, Boas RA. Pharmacokinetic aspects of intravenous anesthesia. *Anesthesiology* 1971; **34**: 538–549.
2. Tucker GT. Pharmacokinetics of local anaesthetics. *British Journal of Anaesthesia* 1986; **58**: 717–731.
3. Kragh-Hansen U. Molecular aspects of ligand binding to serum albumin. *Pharmacological Reviews* 1981; **33**: 17–53.
4. McNamara PJ, Slaughter RL, Pieper JA, Wyman MG, Lalka D. Factors influencing serum protein binding of lidocaine in humans. *Anesthesia and Analgesia* 1981; **60**: 395–400.
5. Mather LE, Tucker GT. Meperidine and other basic drugs: general method for their determination in plasma. *Journal of Pharmaceutical Sciences* 1974; **63**: 306–307.
6. Mancini G, Carbonara AO, Heremans JF. Immunochemical quantitation of antigens by single radial immunodiffusion. *Immunochemistry* 1965; **2**: 235–254.
7. Doumas BT, Watson WA, Biggs HG. Albumin standards and the measurement of serum albumin with bromocresol green. *Clinica Chimica Acta* 1971; **31**: 87–96.
8. Korbon GA, Rowlingson JC, DiFazio CA. Sensitivity to pain predicts CNS sensitivity to lidocaine. *Anesthesiology* 1984; **61**: 767–769.
9. Routledge PA, Stargel WW, Kitchell BB, Barchowsky A, Shand DG. Sex-related differences in the plasma protein binding of lignocaine and diazepam. *British Journal of Clinical Pharmacology* 1981; **11**: 245–250.
10. Swinyard, EA. Analgesics and antipyretics. In: Gennaro AR, ed. *Remington's Pharmaceutical Sciences*. 17th edn. Easton, PA: Mack Publ. Co., 1985; 1101–1102.
11. Adotey J. *Studies on the Interactions of Lidocaine with Plasma Proteins*. Pittsburgh, Pennsylvania: Duquesne University, 1985, Doctoral thesis.
12. Denson DD, Myers JA, Thompson GA, Coyle DE. The influence of diazepam on the serum protein binding of bupivacaine at normal and acidic pH. *Anesthesia and Analgesia* 1984; **63**: 980–984.
13. Scott DB. Toxic effects of local anaesthetic agents on the central nervous system. *British Journal of Anaesthesia* 1986; **58**: 732–735.

Br. J. Anaesth. (1988), **61**, 135–138

EFFECT OF DEXTROSE CONCENTRATION ON THE INTRATHECAL SPREAD OF AMETHOCAINE

A. LEE, D. RAY, D. G. LITTLEWOOD AND J. A. W. WILDSMITH

SUMMARY

Effects of solutions of 0.5% amethocaine, containing different concentrations of dextrose (0%, 1.25%, 2.5% and 5%) were studied after intrathecal injection. The cephalad extent of block was greater with all three dextrose-containing solutions (T6), compared with the isobaric solution which contained no dextrose (T11). The variability of maximum level of block within each group was similar (seven dermatomes), and the rate of onset to maximum extent of block was the same in all groups. The rate of onset to the T12 dermatome was more rapid in the patients who received solutions containing dextrose. The initial onset of effect of the solution containing 1.25% dextrose was more like that of the isobaric solution than of those containing higher concentrations of dextrose.

One of the most important factors influencing the extent of spread of spinal (subarachnoid) anaesthesia is the baricity of the solution injected [1]. Although baricity may also affect the rate of onset of the block [2], this is less well defined.

Solutions are usually made hyperbaric by the addition of dextrose in concentrations between 5% and 8%. In patients placed supine immediately after injection, such solutions will produce blockade with a mean upper level of T5–6 whereas, with an isobaric solution, the mean level is T9–11 [3]. The ideal spinal solution would produce blockade somewhere between these segmental levels, and would guarantee analgesia of the lower abdomen, but minimize the risk of extensive sympathetic block.

This study was designed to investigate the effects of concentrations of dextrose between 0% and 5% on the intrathecal spread of 0.5% amethocaine. In particular, we wished to see if solutions of specific gravity closer to that of cerebrospinal fluid than are traditionally used provided such intermediate spread.

PATIENTS AND METHODS

Forty patients undergoing spinal anaesthesia for lower limb, urological or hernia surgery gave informed consent for the study, which was approved by the local Ethics Committee. Patients were aged between 18 and 65 yr, and were free of overt cardiorespiratory disease.

The patients received temazepam 10 mg by mouth 1 h before arrival in the anaesthetic room, when a venous cannula was inserted. No fluid was administered. Subarachnoid puncture was performed at the third lumbar space, with the patient in the right lateral position, using a 26-gauge spinal needle (Becton Dickinson). Amethocaine 10 mg in 2 ml was injected over 10 s, all injections being performed by the same anaesthetist. Amethocaine solutions were prepared immediately before injection by dissolving a crystalline preparation (Pontocaine, Winthrop) in different proportions of 0.9% saline and 5% dextrose (table I). This gave solutions that contained 0% (group 1),

TABLE I. *Spinal solutions used. All solutions contained amethocaine 10 mg in 2 ml*

Group	Solution baricity	0.9% NaCl (ml)	5% Dextrose (ml)	Dextrose (%)	Sp. gr. (22 °C)
1	Isobaric	2	0	0	1.006
2	Hyperbaric	1.5	0.5	1.25	1.012
3	Hyperbaric	1	1	2.5	1.019
4	Hyperbaric	0	2	5	1.025

A. LEE, F.F.A.R.C.S.; D. RAY, M.B., CH.B.; D. G. LITTLEWOOD, F.F.A.R.C.S.; J. A. W. WILDSMITH, M.D., F.F.A.R.C.S.; Department of Anaesthetics, Royal Infirmary, Edinburgh EH3 9YW.
Accepted for Publication: November 30, 1987.

TABLE II. *Demographic data (mean ± SD)*

	Group 1	Group 2	Group 3	Group 4
Age (yr)	44 ± 10.6	46 ± 12.3	46 ± 12.8	49 ± 9.2
Height (cm)	170 ± 8.5	169 ± 10.1	170 ± 10.4	165 ± 9.5
Weight (kg)	63 ± 9.5	70 ± 10	71 ± 11.2	67 ± 14.7
Sex (M/F)	4/6	4/6	3/7	3/7

1.25 % (group 2), 2.5 % (group 3) or 5 % (group 4) dextrose, and a constant dose of amethocaine (10 mg). Patients were randomly allocated to receive one of these four solutions, each of which was given to 10 subjects.

As soon as the injection was complete, the patients were turned supine and remained horizontal throughout the study. Analgesia, anaesthesia, motor power, heart rate and arterial pressure were assessed at intervals by a single observer who was unaware of the dextrose content of the solution that had been injected. Assessments were made 2 and 5 min after the injection of the amethocaine, and at 5-min intervals for up to 30 min. Analgesia was defined as the inability to appreciate pinprick; anaesthesia as the inability to appreciate touch. Motor power was recorded using the four-point Bromage scale (0 = no paralysis; 1 = inability to raise extended leg; 2 = inability to flex knee; 3 = inability to flex ankle).

Hypotension or premonitory symptoms thereof (for example, nausea) was treated by the immediate administration of ephedrine 3 mg i.v.

Comparisons between the groups were made using Kruskal–Wallis and Mann–Whitney tests [4].

RESULTS

There were no significant differences between the groups in age, sex, height or weight (table II).

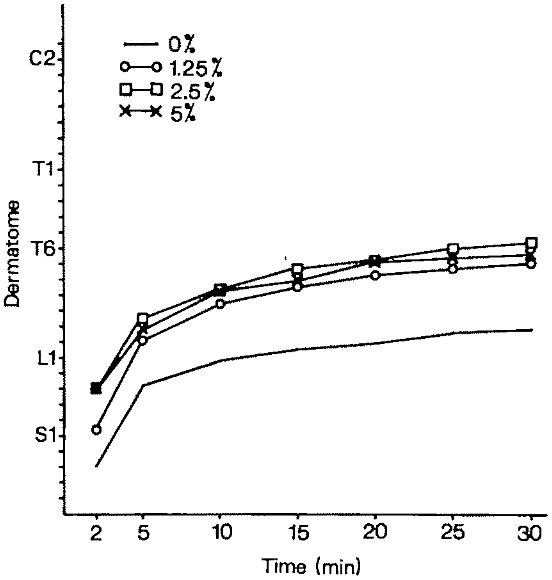


FIG. 1. Mean maximum level of analgesia in the four groups at each assessment.

The maximum extent of analgesia and anaesthesia was greater in groups 2, 3 and 4 compared with group 1 ($P < 0.01$ in each comparison). The median cephalad level of anaesthesia increased with increasing dextrose concentration, but the differences between groups 2, 3 and 4 were small and not significant. One patient in group 1 did not develop anaesthesia, retaining some degree of touch sensation in all dermatomes, but the block was adequate for surgery without further supplementation. Excluding this patient, the range of anaesthetic blocks in group 1 was 7.5 dermatomes, and was comparable to that in the other groups (table III). All patients were included in the statistical analysis.

At each assessment there was a significant

TABLE III. *Maximum height of analgesia and anaesthesia attained in each group of 10 patients. Median, range (one patient in group 1 did not have anaesthesia in any dermatome) and mean ± SD*

	Group 1	Group 2	Group 3	Group 4
Max. height analgesia				
Median	T11	T6	T6	T5.5
Range	T7.5–L3	T4–11	C8–T8.5	T4–10.5
Mean	T11 ± 2.5	T7 ± 2.6	T6 ± 2.2	T7 ± 2.3
Max. height anaesthesia				
Median	L1	T9	T8	T7.5
Range	T8.5–0	T4–11	T4–10.5	T5–11
Mean	L2 ± 4.2	T9 ± 2.5	T8 ± 2.2	T8 ± 2.2

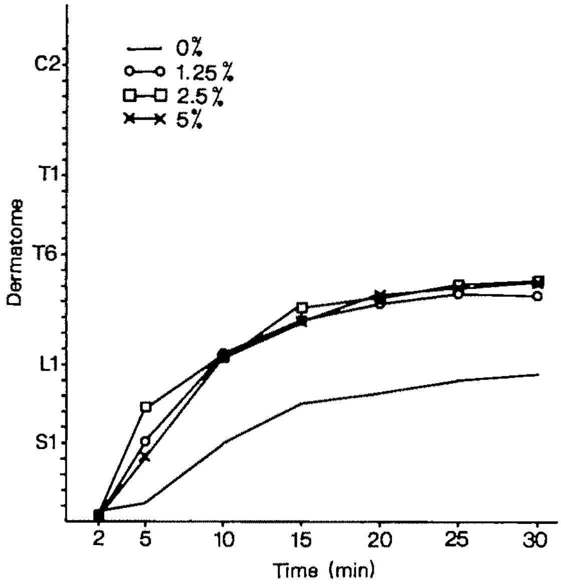


FIG. 2. Mean maximum level of anaesthesia in the four groups at each assessment.

difference between the four groups in extent of analgesia. This was always attributable to differences between group 1 and the others, except at 2 min, when there was no difference between groups 1 and 2. There were no differences in the extent of analgesia between groups 2, 3 and 4 at any time (fig. 1).

From 10 min onwards, there was a significant difference in the extent of anaesthesia, between the four groups. Again this was always as a result of differences between group 1 and the others. There were no differences in the extent of anaesthesia between groups 2, 3 and 4 at any time (fig. 2).

The times taken to develop the maximum levels of analgesia and anaesthesia in each group were not significantly different (table IV). The times taken to develop analgesia and anaesthesia to the T12 dermatome were significantly different between the four groups ($P < 0.01$), being shorter in groups 2, 3 and 4 than in group 1. There were no differences between groups 2, 3 and 4. In group 1, four patients did not develop analgesia to T12 and six patients did not develop anaesthesia to T12. For statistical purposes these patients were assigned a maximum figure of 30 min. One patient in group 1 had a block too limited in spread for the projected surgery and was given a general anaesthetic.

Complete paralysis of both legs occurred in a shorter time with dextrose-containing solutions (table V), but this difference was not significant. Those patients who retained minimal residual movement in the legs were again assigned a figure of 30 min for statistical comparison.

Arterial hypotension requiring treatment occurred in groups 2, 3 and 4 only (table VI).

TABLE IV. *Times (min) to reach maximum analgesia and anaesthesia, and times (min) to reach analgesia and anaesthesia to T12. Median, range and mean ± SD*

	Group 1	Group 2	Group 3	Group 4
Time to T12 analgesia				
Median	20	7.5	5	5
Range	5–30	5–15	2–15	2–10
Mean	19.5±10	8±3	6±4	6±3
Time to T12 anaesthesia				
Median	30	10	10	10
Range	10–30	5–20	5–20	5–20
Mean	24.5±8	11.5±5	10.5±5	12±6
Time to maximum analgesia				
Median	27.5	25	25	22.5
Range	15–30	15–30	15–30	15–30
Mean	25.5±6	25±5	24.5±5	22±5
Time to maximum anaesthesia				
Median	25	20	25	25
Range	15–30	15–30	25–30	20–30
Mean	25±6	22±4	27±3	24.5±4

TABLE V. *Times (min) to complete paralysis of both legs. Median, range and mean ± SD*

	Group 1	Group 2	Group 3	Group 4
Median	20	10	10	5
Range	15–30	5–30	2–30	5–30
Mean	21.5 ± 5.3	14 ± 9.7	14.4 ± 12.2	11.1 ± 10.8

TABLE VI. *Complications*

	Group 1	Group 2	Group 3	Group 4
Hypotension	0	2	4	2
Inadequate block	1	0	0	0

DISCUSSION

This study has confirmed previous work [3] which demonstrated the profound effect of using a solution having a specific gravity greater than that of cerebrospinal fluid. With the numbers involved in each group ($n = 10$) and the relatively wide range of blocks produced, it is possible that small differences between some groups have been underestimated. However, such differences are unlikely to be of any clinical significance, and the numbers studied were sufficient to demonstrate a statistically significant difference between the "isobaric" and other groups. This degree of difference would be of clinical significance and the results are in accord with our previous work [3, 5, 6].

Surprisingly, a solution which was only slightly hyperbaric (1.25 % dextrose) behaved in a manner almost identical to solutions of much greater specific gravity. There is some suggestion that the rate of onset may be influenced by baricity, the solution containing 1.25 % dextrose behaving more like the isobaric solution for the first 2 min, but solutions of specific gravity even closer to that of cerebrospinal fluid would have to be used to investigate this further.

There is at present no spinal solution which will give a predetermined cephalad spread of analgesia, although isobaric amethocaine and hyperbaric solutions give a smaller range of blocks than solutions such as plain bupivacaine [7]. If this range of about seven dermatomes were centred around T8–9, this would be an improvement, giving a more reliable anaesthetic effect with a reduced risk of complications from sympathetic blockade. The mean maximum level of analgesia with all the hyperbaric solutions in this study was T6–7, and it may be that solutions with a specific gravity even closer to that of cerebrospinal fluid would behave in a similar fashion because of the curves of the spinal canal. There is some suggestion from this study that very slightly hyperbaric solutions may spread as far cephalad, but do so more slowly. This might allow time for compensation to occur for the slowly increasing sympathetic blockade, and reduce the incidence of overt effects [8].

Spinal solutions of the specific gravity used in this study do not give blocks in which the mean cephalad spread is lower than that associated with the use of commercially available products. It is not apparent why present hyperbaric spinal solutions have a specific gravity and tonicity far exceeding that of cerebrospinal fluid, as this would appear to be unnecessary. The use of solutions containing even lower concentrations of dextrose may merit investigation.

ACKNOWLEDGEMENTS

The authors wish to thank Dr R. Elton, Statistical Department, University of Edinburgh for his advice, and are grateful for the co-operation of nursing and surgical colleagues during the study.

REFERENCES

1. Wildsmith JAW, Rocco AG. Current concepts in spinal anesthesia. *Regional Anesthesia* 1985; **10**: 119–124.
2. Chambers WA, Edstrom HH, Scott DB. Effect of baricity on spinal anaesthesia with bupivacaine. *British Journal of Anaesthesia* 1981; **53**: 279–282.
3. Brown DT, Wildsmith JAW, Covino BG, Scott DB. Effect of baricity on spinal anaesthesia with amethocaine. *British Journal of Anaesthesia* 1980; **52**: 589–595.
4. *SPSS-X*. New York: McGraw Hill Book Co., 1983; 686–693.
5. McClure JH, Brown DT, Wildsmith JAW. Effect of injected volume and speed of injection on the spread of spinal anaesthesia with isobaric amethocaine. *British Journal of Anaesthesia* 1982; **54**: 917–920.
6. Wildsmith JAW, McClure JH, Brown DT, Scott DB. Effects of posture on the spread of isobaric and hyperbaric amethocaine. *British Journal of Anaesthesia* 1981; **53**: 273–278.
7. Logan MR, McClure JH, Wildsmith JAW. Plain bupivacaine: an unpredictable spinal anaesthetic agent. *British Journal of Anaesthesia* 1986; **58**: 292–296.
8. Bromage PR. *Epidural Analgesia*. Philadelphia: W. B. Saunders Co., 1978; 354.

Br. J. Anaesth. (1988), **61**, 139–143

EFFECTS OF POSTURE AND BARICITY ON SPINAL ANAESTHESIA WITH 0.5% BUPIVACAINE 5 ML

A Double-Blind Study

R. W. D. MITCHELL, G. M. R. BOWLER, D. B. SCOTT AND H. H. EDSTRÖM

SUMMARY

In four groups of 10 patients, 0.5% bupivacaine 5 ml was used in spinal anaesthesia for gynaecological surgery. Group 1 received plain solution in the sitting position, group 2 plain solution in the lateral position, group 3 hyperbaric solution in the sitting position and group 4 hyperbaric solution in the lateral position. All patients were returned to the horizontal supine position, the sitting subjects 2 min after, and the lateral subjects immediately after, spinal injection. In each group the mean height of block was to the mid-thoracic segments, but there was no significant difference between the groups. There was, however, considerable scatter within each group. Posture had some effect on the speed of onset of the analgesia, but no significant effect on the final outcome. The use of 0.5% bupivacaine as a test dose in extradural blockade is discussed.

Bupivacaine 0.5% is being used increasingly for spinal (subarachnoid) anaesthesia; indeed, at the time of writing it is the only agent specifically marketed in the U.K. for this purpose. The plain solution, and the hyperbaric solution containing 8% glucose, have been studied extensively in this context. Chambers, Edström and Scott [1] reported that, in a volume of 3 ml, the use of hyperbaric solutions resulted in a higher spread of block; the use of the plain solution failed to guarantee a block above the lumbar roots.

Many workers have commented on the unpredictability of spread obtained with this agent, especially in the plain formulation [2–4]. Posture has been stated to have some effect on the extent of block with the plain formulation [5] which is, in fact, slightly hypobaric, with a specific gravity of 0.998 at 37 °C.

As doses in the range 2–4 ml with the hyperbaric solution seem to have only a minor effect on spread [6], it may be that 5 ml can produce more consistent results without the danger of unduly widespread spinal block.

The present study was undertaken to examine the effect of larger volumes of these agents in spinal anaesthesia, and to determine the effects of posture and baricity at this volume.

PATIENTS AND METHODS

The study was approved by the regional Ethics of Medical Research Committee and the patients gave verbal consent to participate. Forty female patients who were to undergo major elective gynaecological surgery were studied. They were free of major cardiorespiratory disease and were within the age range 25–57 yr.

Premedication was with diamorphine 5 mg and atropine 0.6 mg i.m. within 1.5 h of the induction of anaesthesia. An i.v. cannula was inserted and a slow infusion of balanced electrolyte and glucose solution (Plasmalyte 148, Baxter–Travenol) was commenced. No attempt was made to "pre-load" the patient's circulation.

Lumbar puncture was performed at the third lumbar space with a 25-gauge spinal needle and the solution was injected at approximately 0.25 ml s^{-1}.

R. W. D. MITCHELL, M.B., CH.B., F.F.A.R.C.S.ENG.; G. M. R. BOWLER, M.B., CH.B., F.F.A.R.C.S.ENG.; D. B. SCOTT, M.D., F.R.C.P.(E.), F.F.A.R.C.S.ENG.; Department of Anaesthetics, Royal Infirmary of Edinburgh, Lauriston Place, Edinburgh EH3 9YW. H. H. EDSTRÖM, PH.D., Astra Läkemedel AB, S-151 85 Södertälje, Sweden. Accepted for Publication: January 9, 1987.

Patients were allocated at random to four groups of 10 patients in each: group 1 received 0.5% plain bupivacaine 5 ml in the sitting position maintained for 2 min and then placed supine; group 2 received 0.5% plain bupivacaine 5 ml in the right lateral position and were immediately turned supine; group 3 received 0.5% bupivacaine 5 ml in 8% glucose in the sitting position maintained for 2 min; group 4 received 0.5% bupivacaine 5 ml in 8% glucose in the lateral position and were immediately turned supine.

The degree and extent of block were assessed by an observer who had no knowledge of the solutions or postures used. The following observations were made at 6, 8, 10, 15, 20 and 30 min after injection:

(a) Upper level of analgesia to pinprick.

(b) Motor block in the legs, using a modified Bromage scale (0 = ability to raise extended leg against gravity; 1 = inability to raise extended leg; 2 = inability to flex the knee; 3 = inability to flex the ankle—complete motor block).

(c) Arterial pressure and heart rate (Dinamap 8146 automated oscillometric monitor).

(d) Any untoward reactions were also noted.

On completion of the study period, the patient was prepared for surgery, which was performed under either light general anaesthesia with thiopentone, nitrous oxide and 0.5% halothane or 0.6% enflurane, or deep sedation with i.v. chlormethiazole.

Statistical analysis was performed using the Kruskal–Wallis test (chi-square approximation) and differences between frequencies by the chi-square test, followed by pair-wise comparisons between groups, where applicable.

RESULTS

Patient data are shown in table I. All groups were comparable in age, weight and height.

Sensory block. The mean (±SEM) interval until the cephalad spread was maximal varied from 18.8 (±2.3) min in group 4 to 22.2 (±2.8 min) in group 1. The mean upper level of block in all groups after 30 min was to the mid-thoracic segments (T4–6). Those groups receiving hyperbaric solution achieved a block one to two segments higher than those receiving plain solution, but these differences were not statistically significant. There was considerable scatter of results within each group (fig. 1). No group exhibited greater consistency than any of the others.

TABLE I. *Details (mean ± SD) of the four groups of patients*

	Group 1	Group 2	Group 3	Group 4
n	10	10	10	10
Age (yr)	45±6	40±10	37±9	38±5
Wt (kg)	64±11	61±9	64±10	59±6
Height (cm)	161±7	162±6	163±6	163±9

One patient in group 4 had a final upper level of analgesia to T11, but there was some difficulty in determining anatomical dermatomes in this patient, whose umbilicus was very close to the xiphisternum.

Onset of block (fig. 2). The sitting position made no significant difference to the ultimate height of block with either the hyperbaric or plain solutions. However, with the plain solutions, the initial onset of the block was significantly faster ($P < 0.01$) in the sitting group. With the hyperbaric groups, the onset was slower in the sitting patients, but this difference was not statistically significant.

Motor block. Figure 3 shows the percentage of patients with complete motor block of the lower limbs after 30 min (Bromage grade 3). Thirty-eight patients developed complete motor block of the lower limbs. The two remaining patients were able only to flex the ankles; one received the plain solution, one the hyperbaric solution. The onset time to complete motor block was shorter (ns)

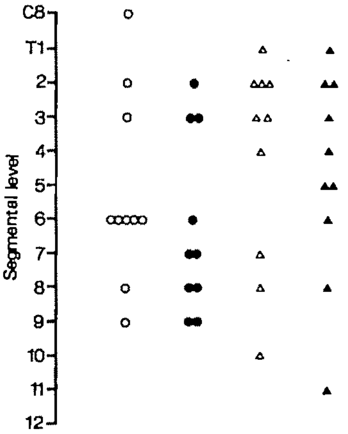


FIG. 1. Cephalad spread of sensory block 30 min after subarachnoid injection of 0.5% bupivacaine 5 ml at L3–4. n = 10 in each group. ○ = Group 1: plain, sitting. ● = Group 2: plain, lateral. △ = Group 3: hyperbaric, sitting. ▲ = Group 4: hyperbaric, lateral.

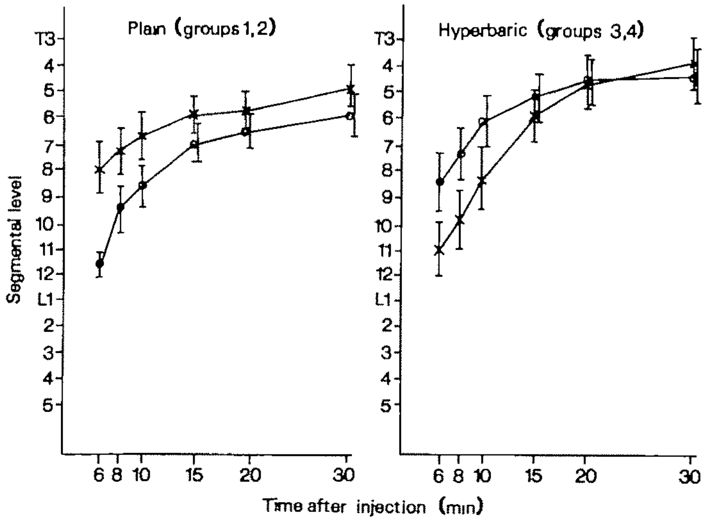


FIG. 2. Onset of sensory block to pinprick after subarachnoid injection of 0.5% bupivacaine 5 ml at L3–4. Mean ±SEM. $n = 10$ in each group. × = Sitting; ○ = lateral.

with the hyperbaric solution, varying from a mean (±SEM) of 9.5 (±1.3) min in group 4 to 11.6 (±1.4) min in group 2. The mean onset time to grade 1 motor block was 6 min in all groups.

All patients had an adequate block for the proposed surgical procedure. Thirty-two patients underwent lower abdominal surgery and eight underwent vaginal operations. Abdominal relaxation was satisfactory in those patients who underwent lower abdominal surgery although two patients, one each from groups 2 and 4, required a small dose of a neuromuscular blocking drug at the end of surgery to assist peritoneal closure (2 h after the spinal injection).

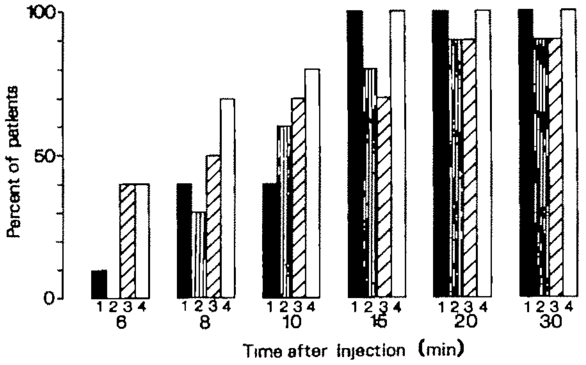


FIG. 3. Complete motor block. Percentage of patients unable to flex ankle joint after subarachnoid injection of 0.5% bupivacaine 5 ml at L3–4. $n = 10$ in each group. Group 1 = plain, sitting; group 2 = plain, lateral; group 3 = hyperbaric, sitting; group 4 = hyperbaric, lateral.

Those patients undergoing abdominal operations were provided with postoperative pain relief by means of a continuous infusion of bupivacaine delivered through an extradural catheter inserted at the T11–12 space at the end of surgery. For this reason we have no data on the duration of the subarachnoid block in these patients.

Untoward effects. Six patients (two in the plain groups, four in the hyperbaric groups) received ephedrine 10–15 mg i.v. for hypotension (systolic arterial pressure less than 80 mm Hg, or lesser degrees of hypotension accompanied by bradycardia or nausea).

Four patients developed the typical features of "post-spinal headache" in the subsequent few days: three required an autologous extradural blood patch, which was immediately effective in all cases.

DISCUSSION

McClure, Brown and Wildsmith [7] showed that the range of block obtained with isobaric amethocaine was narrower when the chosen dose of drug was injected in a small volume. However, with plain bupivacaine, no significant improvement in predictability was found with equal doses of the drug given as 0.75% compared with 0.5% solutions [4].

Chambers, Edström and Scott [1], using 3 ml of 0.5% bupivacaine, showed that hyperbaric solutions were more suitable for abdominal surgery, since the plain solution frequently failed to achieve a sufficient height of block. With 3 ml of plain solution given in the lateral position the mean height of block was T10. In this study, 5 ml of plain solution resulted in a mean height of block to T6, which should be satisfactory for lower abdominal surgery. Such an increase in the height of block was not seen with the hyperbaric solution. In the lateral position, the corresponding height of block was T5 with 3 ml and T4–5 with 5 ml.

Using the larger dose of 5 ml did not increase predictability in an individual patient with either the plain or the hyperbaric solutions as we had hoped. Some patients in both groups had an upper level of block which would be considered barely adequate for lower abdominal surgery (although in the event it was adequate), while others had blocks which were a good deal higher than necessary. However, the high blocks were not accompanied by significant respiratory paralysis or marked hypotension.

The adequacy of muscle relaxation for abdominal surgery in this study contrasts with the observations of Chambers, Edström and Scott [1] that, in six of eight patients who received 3 ml of the plain solution, relaxation was inadequate. The increase in dose to 5 ml thus makes the plain solution more suitable for abdominal surgery.

It is of interest that neither baricity nor position had any statistically significant effect on the spread of bupivacaine in this volume. While Axelsson, Edström and Widman [8] showed a clear dose–response relationship with the plain solution in volumes of 1.5–4 ml, and Axelsson and colleagues [9] found a similar response with the hyperbaric solution in patients, we have shown little or no difference in spread between 2, 3 and 4 ml of the hyperbaric solution [6]. It is possible that, with a volume of 5 ml, the effects of volume *per se* overtake those of baricity and posture, thus accounting for the observed similarities between the groups.

There now exists some evidence that, if posture is to be used to control the ultimate spread of solutions in spinal anaesthesia, the chosen posture must be maintained for much longer than 2 min [10]. However, in those patients in whom a mid-thoracic block is expected, the maintenance of the sitting posture may be attended by an unacceptable degree of hypotension as blood is pooled in the lower limbs as sympathetic block develops.

We did not determine the duration of spinal blockade in this study, but previous work [6, 9] has indicated that increasing the dose of local anaesthetic in spinal anaesthesia increases the duration of blockade. It is reasonable, then, to expect that 5-ml injections will last longer than 4-ml ones.

If L3–4 spinal anaesthesia with 0.5% bupivacaine is to be used for lower abdominal surgery, plain solution in a 3-ml dose would be unsuitable because of inadequate relaxation of the abdominal muscles, although the same volume of the hyperbaric solution would usually be adequate [1]. From this study, 5 ml of plain solution provides a more adequate sensory block than 3 ml of hyperbaric solution, the block always being to T9 or higher with the former. There was little to choose between injection in the sitting position maintained for 2 min or the lateral position. An inadequate height of sensory block could be associated with the use of plain 0.5% bupivacaine 4 ml [4]. The choice, therefore, appears to be between 3 ml of hyperbaric bupivacaine and 5 ml of plain bupivacaine. We anticipate that sensory and motor block would last longer with the 5-ml dose. The unpredictability of the height of sensory block might result in excessive cephalad spread with either dose. We should emphasize that all our subjects were gynaecological patients and our results cannot be extrapolated to patients in late pregnancy, when the spread of local anaesthetic solution within the subarachnoid space may be different from that in the non-pregnant state.

The results of the present study are also of interest in regard to the use of test doses in extradural blockade. They show that, even with the large dose of 5 ml, the plain solution of 0.5% bupivacaine did not produce widespread and obvious spinal block by 6 min; approximately 20 min was required on average to approach maximum cephalad spread. Although some degree of blockade was obvious when the patient was adequately tested, reliance on voluntary movement only would have failed to reveal the subarachnoid injection: 95% of patients who received plain bupivacaine were able to flex the ankle after 6 min, and 50% after 10 min. Although complete motor block was present early in a greater proportion of patients following hyperbaric bupivacaine, it was not until 20 min after injection that 90% were unable to flex their ankles—a delay similar to that seen with the plain solution. If test doses are to be accurately interpreted, sensory block should be relied upon rather than motor block. Demonstrable analgesia is present in the great majority of patients after 5 min, both with plain and with hyperbaric solutions. However, in some patients demonstrable analgesia may also be present following the injection of 5 ml of local anaesthetic into the extradural space, and thus give a false positive test. We have previously advocated the use of a 2-ml dose of hyperbaric solution to test for subarachnoid injection [11]. Such a test dose, if injected into the subarachnoid space should, after 5 min, give clear indication of a relatively extensive sensory blockade, but would not cause blockade of more than one or two segments if injected into the extradural space.

ACKNOWLEDGEMENTS

We thak Kerstin Danielson and Eva Holmqvist, nurse anaesthetists, for their assistance.

REFERENCES

1. Chambers WA, Edström HH, Scott DB. Effect of baricity on spinal anaesthesia with bupivacaine. *British Journal of Anaesthesia* 1981; **53**: 279–282.
2. Chambers WA. Intrathecal bupivacaine. *British Journal of Anaesthesia*, 1982; **54**: 799–801.
3. Russell IF. Posture and isobaric subarachnoid anaesthesia. *Anaesthesia* 1984; **39**: 865–867.
4. Logan MR, McClure JH, Wildsmith JAW. Plain bupivacaine: an unpredictable spinal anaesthetic agent. *British Journal of Anaesthesia* 1986; **58**: 292–296.
5. Kalso E, Tuominen M, Rosenberg PH. Effect of posture and some CSF characteristics on spinal anaesthesia with isobaric 0.5% bupivacaine. *British Journal of Anaesthesia* 1982; **54**: 1179–1184.
6. Chambers WA, Littlewood DG, Edström HH, Scott DB. Spinal anaesthesia with hyperbaric bupivacaine: effects of concentration and volume administered. *British Journal of Anaesthesia* 1982; **54**: 75–80.
7. McClure JH, Brown DT, Wildsmith JAW. Effect of injected volume and speed of injection on the spread of spinal anaesthesia with isobaric amethocaine. *British Journal of Anaesthesia* 1982; **54**: 917–920.
8. Axelsson KH, Edström HH, Widman GB. Spinal anaesthesia with glucose-free 0.5% bupivacaine: effects of different volumes. *British Journal of Anaesthesia* 1984; **56**: 271–278.
9. Axelsson KH, Edström HH, Sundberg A, Wideman GB. Spinal anaesthesia with hyperbaric 0.5% bupivacaine—effects of volume. *Acta Anaesthesiologica Scandinavica* 1982; **26**: 439–445.
10. Wildsmith JAW, McClure JH, Brown DT, Scott DB. Effects of posture on the spread of isobaric and hyperbaric amethocaine. *British Journal of Anaesthesia* 1981; **53**: 273–278.
11. Bowler GMR, Scott DB. Epidural test dose. *Anaesthesia* 1984; **39**: 945.

Br. J. Anaesth. (1988), **61**, 144–148

SPINAL ANAESTHESIA WITH HYPERBARIC BUPIVACAINE: EFFECTS OF CONCENTRATION AND VOLUME WHEN ADMINISTERED IN THE SITTING POSITION

R. P. ALSTON, D. G. LITTLEWOOD, R. MEEK AND H. H. EDSTRÖM

SUMMARY

In a double blind study, solutions of 0.5% or 0.75% bupivacaine containing 8% dextrose were compared with regard to the effect of varying concentration and volume when administered intrathecally to patients in the sitting position. Ten patients received 3 or 4 ml of 0.5% bupivacaine or 2 or 3 ml of 0.75% bupivacaine. Nine patients received 0.5% bupivacaine 2 ml and another nine received 0.75% bupivacaine 1.3 ml. The use of the 10-mg dose of both solutions was abandoned after nine patients in each group because of insufficient cephalad spread. With both solutions, the smallest volumes (bupivacaine 10 mg) had significantly shorter durations of action than both the larger ones (15–20/22.5 mg), between which there were no significant differences.

Although the effects of concentration and volume have been studied after the administration of hyperbaric bupivacaine for spinal anaesthesia in the lateral position, it is not known if the anaesthetic profile is altered by administration in the sitting position [1]. In addition, debate continues as to whether dose or volume is the main factor influencing spread and duration of sensory loss [2,3]. The present study was undertaken to elucidate the effects of intrathecal administration of different volumes of 0.5% and 0.75% bupivacaine in 8% dextrose to patients in the sitting position.

PATIENTS AND METHODS

Fifty-eight patients undergoing transurethral resection of prostate under spinal (subarachnoid) anaesthesia were studied. Three patients underwent herniorrhaphy and one orchidectomy immediately after the resection of prostate. The study was approved by the Ethical Committee of the Royal Infirmary, Edinburgh. Informed consent was obtained from all patients before their inclusion in the study.

Approximately 1 h after premedication with diazepam 10 mg by mouth, an i.v. infusion was established and, with the patient sitting, lumbar puncture was performed with a 22-gauge needle at the L2–3 or L3–4 space using a midline approach. The patients were allocated randomly to receive 3 ml or 4 ml of 0.5%, or 2 ml or 3 ml of 0.75% bupivacaine containing 8% dextrose, such that 10 patients received each volume of each concentration. Two millilitre of 0.5% solution and 1.3 ml of 0.75% solution was injected in a further nine patients each. Once a free flow of cerebrospinal fluid was obtained, the study solution was injected at a rate of 0.2 ml s^{-1} (without barbotage). The solution injected in each patient was known only to the anaesthetist performing the block. The volumes were chosen to allow comparison between groups with different concentrations, but equivalent doses. It was intended that each volume of each concentration should be given to 10 patients but, for the reasons given below, only nine patients received the lowest

---

R. P. ALSTON†, F.F.A.R.C.S.; D. G. LITTLEWOOD*, F.F.A.R.C.S.; R. MEEK*, F.F.A.R.C.S.; H. H. EDSTRÖM§, PH.D.; Department of Anaesthetics, Royal Infirmary of Edinburgh, Lauriston Place, Edinburgh EH3 9YW. Accepted for Publication: September 1, 1986.

Present addresses:

†University Department of Anaesthesia, Glasgow Royal Infirmary, 8–16 Alexandra Parade, Glasgow G31 2ER.

*Department of Anaesthesia, Dumfries and Galloway Royal Infirmary, Bankend Road, Dumfries DG1 4AP.

§Astra Läkemedel AB, S-151 85 Södertälje, Sweden.

Correspondence to R.P.A., Glasgow.

TABLE I. *Mean (±SEM) age, weight and height of patients*

Bupivacaine solution used	*n*	Age (yr)	Weight (kg)	Height (cm)
0.5%, 2 ml (10 mg)	9	73.4±2.9	72.3±4.0	171±2.2
0.5%, 3 ml (15 mg)	10	69.9±2.9	72.7±2.7	173±2.1
0.5%, 4 ml (20 mg)	10	65.5±2.6	74.3±3.4	175±2.3
0.75%, 1.3 ml (10 mg)	9	66.9±2.3	67.7±1.9	174±3.4
0.75%, 2 ml (15 mg)	10	74.6±2.5	67.7±4.8	173±1.7
0.75%, 3 ml (22.5 mg)	10	74.5±5.3	74.5±5.3	174±2.0

volume of each concentration. The patients were kept sitting for 2 min after injection then placed supine until ready for surgery, when they were placed in the lithotomy position.

The cephalad spread of sensory blockade, the degree of motor blockade of the lower limbs and the arterial pressure and heart rate (Dinamap) were measured during anaesthesia. The levels of sensory blockade were assessed using a blunt needle and were tested along the anterior axillary line on the trunk, the legs and the perineum. Analgesia was defined as loss of sensation of pinprick and anaesthesia as loss of sensation of touch. The degree of motor blockade was assessed on a 0–3 scale (0 = full movement of legs; 1 = inability to raise extended leg; 2 = inability to flex knee; 3 = inability to flex ankle). During the first 30 min of assessment, 500 ml of Hartmann's solution was infused.

If hypotension required treatment, ephedrine or methoxamine was given. Patients were questioned 1–2 days after the operation, about the occurrence of adverse effects and, in particular, about headache.

The results were analysed using Wilcoxon rank tests or Irwin–Fischer exact test, where appropriate. $P < 0.05$ was considered statistically significant.

RESULTS

There were no statistically significant differences between the mean ages, weights and heights of patients in the six groups (table I).

Sensory loss

Onset time for maximal spread of analgesia was generally short, the mean times varying from 17 to 30 min, with no differences between the groups (table II; figs 1, 2).

TABLE II. *Mean (±SEM) time (min) for maximum cephalad spread of analgesia. Differences not statistically significant*

Bupivacaine solution used	Time (min)
0.5%, 2 ml (10 mg)	30±11.5
0.5%, 3 ml (15 mg)	22±4.4
0.5%, 4 ml (20 mg)	20±1.6
0.75%, 1.3 ml (10 mg)	18±3.7
0.75%, 2 ml (15 mg)	26±7.3
0.75%, 3 ml (22.5 mg)	23±2.1

Bupivacaine 0.5% produced a statistically significant increase in cephalad spread with increasing volume between 2 ml and 4 ml ($P < 0.05$) and 3 ml and 4 ml ($P < 0.05$), but not

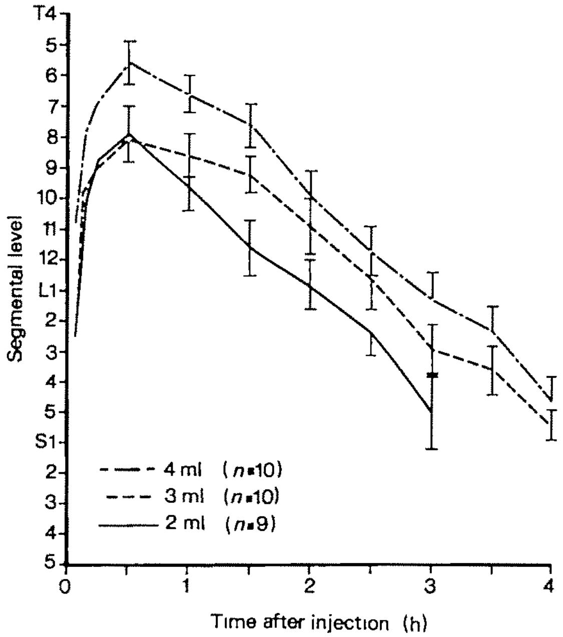


FIG. 1. Mean (±SEM) cephalad spread of analgesia after administration of different volumes of 0.5% bupivacaine in 8% dextrose. There is a statistically significant difference in maximum cephalad spread between 2 ml and 4 ml and between 3 ml and 4 ml ($P < 0.05$).

between 2 ml and 3 ml. With 0.75 % bupivacaine, increasing volume produced a statistically significant increase in cephalad spread between 1.3 ml and 2 ml ($P < 0.05$) and 1.3 ml and 3 ml ($P < 0.01$), but not between 2 ml and 3 ml. No statistically significant differences were found when comparing the 15-mg and 20/22.5-mg doses, but 2 ml of 0.5 % bupivacaine produced a significantly ($P < 0.05$) higher cephalad spread than 1.3 ml of 0.75 % bupivacaine.

The spread of anaesthesia was on the average two or three segments lower than that of analgesia.

Motor blockade

Statistically significant differences in regard to onset times to complete motor blockade were found between 10 mg and 20/22.5 mg; that is, between the smallest and the largest doses. When comparing equal doses, no differences were found between the solutions. Motor blockade degree 1 and 2 was seen in nine of nine and eight of 10 patients given 0.5 % bupivacaine and in six of nine and four of nine patients given 0.75 % bupivacaine. Complete motor blockade of the lower limbs occurred in eight and 10 patients in the larger dose groups (15 mg and 20/22.5 mg), but only in six of nine and two of nine of the patients given 0.5 % bupivacaine 2 ml and 0.75 % bupivacaine 1.3 ml, respectively (table III). No differences in the frequency of the degrees of motor blockade were found in the 0.5 % bupivacaine groups. In the 0.75 % bupivacaine groups, statistically significant differences were found for all degrees (1–3) of motor blockade between 1.3 ml and 2 ml and between 1.3 ml and 3 ml, but not between 2 ml and 3 ml.

Duration

With both 0.5 % and 0.75 % bupivacaine, increasing the dose from 10 mg to 15 mg (but not from 15 mg to 20/22.5 mg) produced a significantly longer total duration of analgesia (figs 1, 2). Mean duration of analgesia in the thoracic segments and total duration of analgesia (that is, until no sensory loss could be detected) are shown in table IV. No significant differences were found when equivalent doses were compared.

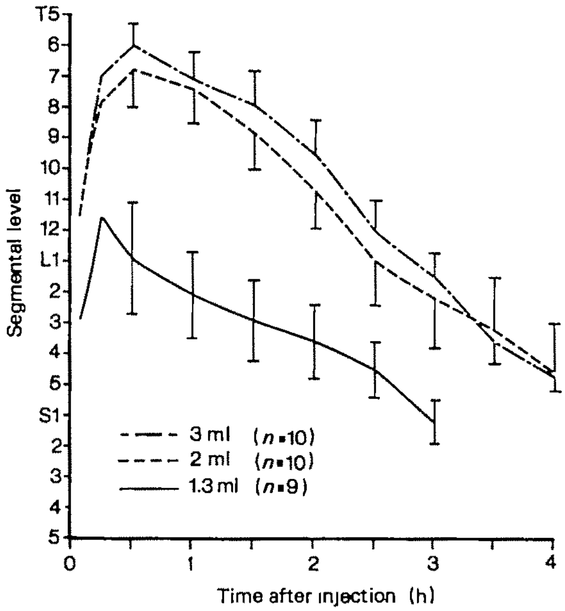


FIG. 2. Mean (± SEM) cephalad spread of analgesia after administration of different volumes of 0.75 % bupivacaine in 8 % dextrose. There is a statistically significant difference in maximum cephalad spread between 1.3 ml and 2 ml ($P < 0.05$) and 3 ml and 1.3 ml ($P < 0.01$).

With the 0.5 % bupivacaine solution, duration of motor blockade tended to increase with increasing dose. Statistically significant differences in duration of complete motor blockade were found between the 2-ml group and both the 3- and 4-ml groups ($P < 0.01$). No differences could be ascribed to the different volumes of 0.75 % bupivacaine. When equal doses were compared, no significant differences were found between the solutions.

TABLE III. *Mean (± SEM) onset time (min) and frequency of complete motor blockade of the lower limb*

	0.5 % Bupivacaine			0.75 % Bupivacaine		
	2 ml	3 ml	4 ml	1.3 ml	2 ml	3 ml
Onset (min)	18.7±2.2	15.3±2.5	11.7±1.9	18.0±2.0	13.4±2.7	8.9±0.9
P		< 0.05			< 0.05	
Frequency	6/9	8/10	9/10	2/9	8/10	10/10
P				< 0.05		
					< 0.01	

TABLE IV. *Mean (± SEM) duration (min) of analgesia in the thoracic segments, and total duration of block (i.e. until no sensory loss could be detected)*

	0.5 % Bupivacaine			0.75 % Bupivacaine		
	2 ml	3 ml	4 ml	1.3 ml	2 ml	3 ml
Thoracic segments	148±26	138±15	158±15	51±19	139±19	156±14
P				└ < 0.05 ┘ (1.3 ml vs 2 ml)		
				└ < 0.01 ┘ (1.3 ml vs 3 ml)		
Total	238±20	299±19	315±20	213±29	297±16	324±20
P	└ < 0.05 ┘ (2 ml vs 3 ml)			└ < 0.05 ┘ (1.3 ml vs 2 ml)		
	└ < 0.05 ┘ (2 ml vs 4 ml)			└ < 0.01 ┘ (1.3 ml vs 3 ml)		

Quality of anaesthesia

Two patients who received 0.75 % bupivacaine 1.3 ml had insufficient analgesia as a result of minimal cephalad spread. One of these required general anaesthesia and, as a result of this, this dose group was omitted from the rest of the study. One patient given 0.75 % bupivacaine 2 ml had sufficient analgesia for transurethral resection of prostate, but not for the subsequent herniorrhaphy, and required i.v. papaveretum. One patient given 0.75 % bupivacaine 3 ml complained of discomfort on bladder distention and required general anaesthesia, despite analgesia to T8–9.

In the group given 0.5 % bupivacaine 2 ml, two patients had insufficient analgesia and required general anaesthesia. One had an initial block to L4 that spread to L1 by 30 min and T12 by 120 min, which was satisfactory for transurethral resection of prostate, but not for the orchidectomy that followed. The other, despite a block to T8, had lower right abdominal pain which was unrelieved by i.v. papaveretum. This dose group also was omitted for the rest of the study. Two patients who received 0.5 % bupivacaine 3 ml had insufficient analgesia. One, with a block to T7, had good analgesia for 130 min but, because of prolonged surgery, required general anaesthesia at that time. The other only had spread to T11 and required i.v. papaveretum to relieve an aching sensation. All patients given 0.5 % bupivacaine 4 ml had sufficient analgesia for surgery.

Cardiovascular changes

Arterial pressure and heart rate did not differ statistically significantly between the groups before blockade. The systolic and diastolic arterial pressures decreased by 10–20 % on the average in each group, and heart rate, which initially increased by approximately 5 %, then decreased by approximately 10 % after 20 min. No statistically significant differences were found between the groups.

Four patients received ephedrine and seven methoxamine for treatment of hypotension. All but one had spread to T8 or above and were equally distributed among the groups.

Adverse effects

No adverse effects were noted in this study.

DISCUSSION

Increasing the volume of 0.5 % bupivacaine from 2 to 3 ml did not increase the cephalad spread of analgesia, whereas increasing the volume from 3 to 4 ml did. This is the contrary of the results reported by Axelsson and colleagues [4]. It is difficult to explain the differences as the techniques used were similar, but it might, perhaps partly result from borderline statistical significances (in both directions) in both studies.

When hyperbaric 0.5 % bupivacaine is given to patients in the sitting position, there seems to be a certain relationship between the dose and the cephalad spread. This does not seem to occur when the same solution and volumes/doses are used for spinal anaesthesia in patients in the supine position. With 0.5 % bupivacaine, increases of the volume administered (from 2 to 4 ml) had no effect on the cephalad spread of analgesia, whereas with 0.75 % bupivacaine, increasing the volume administered resulted in a statistically greater spread [1]—again opposite to the results of the present study.

Sitting the patient for administration of hyperbaric bupivacaine does change the profile of anaesthetic effect, although it is possible that the lithotomy position also has an influence. Apart from ease of performance of lumbar puncture and patient comfort during its performance, the main advantage of the sitting position is the possibility of limiting the spread to the mid-thoracic dermatomes, as has been shown in the present study, using 15–20/22.5 mg. On the other hand, doses of 10 mg seem to be disadvantageous in terms of spread and duration of analgesia.

From our results, the use of hyperbaric 0.75% bupivacaine for spinal anaesthesia appears to confer no advantages over hyperbaric 0.5% bupivacaine, as has also been shown by Chambers and colleagues [1].

In the present study, when equivalent doses were compared, the only significant difference was found at the 10-mg dose, where 0.5% bupivacaine 2 ml spread higher than 0.75% bupivacaine 1.3 ml.

With regard to duration of analgesia, both solutions acted similarly, in that the lowest dose (10 mg) of each concentration was significantly shorter acting than both of the higher doses (15 mg, 20/22.5 mg)—between which no significant differences were found. When equivalent doses were compared, there was no significant difference except at the 10-mg dose when 0.75% bupivacaine 1.3 ml lasted for a significantly shorter time than 0.5% bupivacaine 2 ml at L2. Evidently, the posture of the patient, together with the volume and, possibly, concentration of the local anaesthetic, affect the cephalad spread of the spinal blockade when hyperbaric solutions of bupivacaine are used.

REFERENCES

1. Chambers WA, Littlewood DG, Edström HH, Scott DB. Spinal anaesthesia with hyperbaric bupivacaine: effects of concentration and volume administered. *British Journal of Anaesthesia* 1982; 54: 75–80.
2. Nolte H, Stark P. Die Dosis–Wirkungs-relation isobaren Bupivacain zur spinal Anaesthesie. *Regional Anaesthesie* 1979; 2: 1–4.
3. Tuominen M, Kalso E, Rosenberg PH. Effects of posture on spread of spinal anaesthesia with isobaric 0.75% or 0.5% bupivacaine. *British Journal of Anaesthesia* 1982; 54: 313–318.
4. Axelsson KH, Edström HH, Sundberg AEA, Widman GB. Spinal anaesthesia with hyperbaric 0.5% bupivacaine: effects of volume. *Acta Anaesthesiologica Scandinavica* 1982; 26: 439–445.

Br. J. Anaesth. (1988), **61**, 149–153

EXTRADURAL BUPIVACAINE OR LIGNOCAINE ANAESTHESIA FOR ELECTIVE CAESAREAN SECTION: THE ROLE OF MATERNAL POSTURE

J. A. REID AND J. THORBURN

SUMMARY

Extradural anaesthesia was induced in 64 patients in either the sitting or the lateral position, for elective Caesarean section with either 0.5% plain bupivacaine or 2% lignocaine with adrenaline 1 in 200000. Onset was significantly shorter and a significantly greater number of patients were ready for surgery within 35 min following injection of lignocaine in the lateral position. Hypotension (defined as a 25% or greater reduction in arterial pressure) occurred in 36% of patients. Significantly more patients who had received the first injection of local anaesthetic agent in the sitting position required ephedrine to correct maternal hypotension. Most frequently, hypotension coincided with transfer of patients to theatre and thus was associated with movement of the patient in the presence of extensive sympathetic block.

Bupivacaine 0.5% plain is the most commonly used agent for Caesarean section under extradural block in the U.K. In 1984, Dutton and colleagues [1] studied 0.75% bupivacaine, but found that it offered no advantages over 0.5% bupivacaine plain. Other local anaesthetic agents have been used in the past. In 1962 Bromage [2] demonstrated that the rate of spread of extradural 2% lignocaine with adrenaline 1 in 200000 was faster than that of 0.5% bupivacaine. This advantage was outweighed by evidence from neurobehavioural studies which found neonates to be floppy although alert, when the mothers had received extradural lignocaine for analgesia in labour [3]. However, several more recent studies have failed to confirm adverse neonatal effects when extradural lignocaine was used for Caesarean section [4–6].

The influence of maternal position on the extradural blockade produced for Caesarean section is uncertain. In non-pregnant patients, the lateral position favours more rapid and more extensive spread, and increased duration of action of the extradural blockade on the dependent side [7]. These effects have been confirmed in pregnant patients in labour [8]. Other authors, using extradural bupivacaine for both labour and Caesarean section, have shown the sitting position to reduce the extent of segmental spread, but this was not considered to be of sufficient magnitude to be clinically significant [2, 9, 10]. However, Hodgkinson and Hussain [11] found the sitting position limited segmental spread only in obese patients.

This study was designed to compare bupivacaine and lignocaine and the effect of maternal posture in patients undergoing extradural anaesthesia using a catheter technique for elective Caesarean section.

PATIENTS AND METHODS

Local Ethics Committee approval and patient consent were obtained. All patients in the study had selected extradural anaesthesia for their elective Caesarean section. Routine preoperative preparation included overnight fasting and ranitidine 150 mg by mouth the night before and the morning of surgery. On the patient's admission to the labour suite, a cannula was inserted into a forearm or hand vein and baseline values of maternal heart rate and arterial pressure and fetal heart rate were recorded. One litre of Ringer's Lactate solution was infused during the 15 min

LIBRARY

Joyce A. Reid, F.F.A.R.C.S.; John Thorburn, F.F.A.R.C.S.; Department of Anaesthesia, Western Infirmary, Dumbarton Road, Glasgow. Accepted for Publication: January 13, 1988.

before an extradural catheter was sited at L2–3 or L3–4 under sterile conditions.

The volume of the first injection of local anaesthetic solution was related to the patient's height: less than or equal to 1.52 m, 10 ml; 1.52–1.71 m, 13 ml; greater than 1.71 m, 17 ml. The extradural injection was performed with the patient in either the sitting or the lateral position. Maternal heart rate and arterial pressure and fetal heart rate were recorded at 5-min intervals, or every 1 min if hypotension occurred. The time interval between the first extradural injection and maximal reduction in maternal arterial pressure was noted.

Sixty-four patients were allocated randomly to one of four groups. Group 1 patients received the initial extradural injection of 0.5% plain bupivacaine in the sitting position. Group II patients also received 0.5% bupivacaine, but all injections were given with the patient in the lateral position. Group III patients received the initial injection of 2% lignocaine with adrenaline 1 in 200000 while in the sitting position. Group IV patients received all injections of the same drug in the lateral position.

The management of patients in groups I and III and groups II and IV was identical. The sitting position was maintained for a minimum of 10 min unless hypotension or dizziness developed, when the patient was placed in the lateral position. All subsequent top-up injections were given to patients in the lateral supine position. Hypotension was defined as a 25% or greater reduction in arterial pressure and this was regarded as an indication for administration of i.v. ephedrine. Episodes of hypotension were recorded from the time of initial injection until delivery of the baby. Observations of the effect of the initial injection and subsequent management were undertaken by a second anaesthetist who was unaware of the local anaesthetic agent used.

The spread of the sensory blockade was assessed by altered skin sensation to pinprick. The extent of motor block was noted also. These assessments were carried out at 5-min intervals following extradural injection, by the second anaesthetist. Further top-up doses of local anaesthetic agent were given when the effect of the previous injection became apparent and the timing and volumes of the injection noted. This technique reflects current practice.

The time taken to establish a satisfactory block from T5–6 to S5 was recorded as the time until ready for surgery. Immediate transfer of the mother to the operating theatre was not always possible, but was undertaken following a variable, but generally short delay. The operating table was positioned with a left lateral tilt of 10–15° until delivery, to avoid aortocaval compression. Supplements of inhalation or i.v. agents, or both, were given as appropriate, and in one patient conversion to general anaesthesia by rapid sequence induction was required. Adjuvants used included fentanyl, papaveretum and diazemuls, which reflects our current practice.

Data were analysed statistically by analysis of variance, Student's *t* test, Chi squared test and Pearson's *r* correlation coefficient, where appropriate. A *P* value of less than 0.05 was considered significant.

RESULTS

There was no significant difference in age, weight and height for all patients in each of the four groups (table I).

Fourteen of the 16 patients who received 2% lignocaine with adrenaline 1 in 200000 while lying in the left lateral position, were ready for surgery in less than 35 min. This result was significantly different from the other groups ($P < 0.05$). Similarly, the time to readiness for surgery was more

TABLE I. *Patient data (mean ± SD)*

	Bupivacaine		Lignocaine		*P*
	Sitting	Lying	Sitting	Lying	(all groups)
Number of patients	16	14	18	16	
Age (yr)	30 ± 4.4	28 ± 5.1	29 ± 6.3	31 ± 5.9	ns
Weight (kg)	72 ± 14.4	63 ± 12.4	70 ± 13.7	72 ± 9.0	ns
Height (m)	1.59 ± 0.09	1.58 ± 0.09	1.59 ± 0.04	1.62 ± 0.07	ns

TABLE II. *Onset time, dose of extradural drugs and requirement for sedation/analgesia (mean ± SD).* †*No significant difference between groups.* **$P < 0.05$ compared with other groups*

	Bupivacaine		Lignocaine	
	Sitting	Lying	Sitting	Lying
Number of patients	16	14	18	16
Total dose (mg)†	119.15 ± 26.84	110.38 ± 22.86	457.5 ± 94.34	415 ± 97.87
Onset time (min)	51.25 ± 15.7	43.31 ± 14.2	42.69 ± 17.21	29.53 ± 8.7*
Number ready within 35 min	3	5	7	14*
Number receiving analgesia†	7	2	4	1
Number receiving sedation†	4	1	4	1

TABLE III. *Incidence and degree of hypotension (mean ± SD).* **Combined number of sitting patients given ephedrine significantly greater ($P < 0.05$) than combined number lying. No other significant differences. SAP = Systolic arterial pressure*

	Bupivacaine		Lignocaine	
	Sitting	Lying	Sitting	Lying
Total number (each group)	16	14	18	16
Time sitting (min)	15.25 ± 7.4		10.06 ± 2.79	
Change in SAP (patients not given ephedrine) (mm Hg)	16.3 ± 5.5	16.7 ± 7.1	17.4 ± 12.4	18.4 ± 12.4
Patients given ephedrine				
Number	10*	3	6*	4
Change in SAP (mm Hg)	44.4 ± 20.1	55.6 ± 23.8	40.68 ± 14.0	36.25 ± 23.8
Change in SAP (%)	36.02% ± 13.81		31.61% ± 9.69	

consistent in the patients who received lignocaine in the lateral position (table II).

When patients received the local anaesthetic agents in the lateral position, fewer in each group required additional analgesic drugs during surgery than those who received extradural injections in the sitting position, although the difference was not statistically significant (table II).

There was no significant difference between the average total dose of each drug administered to patients in the sitting and lying positions, but patients in the sitting position received larger doses of local anaesthetic.

A brief, but frequently profound episode of hypotension was a common occurrence in all groups. Twenty-three of the 64 patients required ephedrine in addition to i.v. fluids. Hypotension occurred more commonly in patients who had received bupivacaine in the sitting position, but this difference was not significant (table III). There was no significant difference in the percentage of reduction in arterial pressure or in requirements for ephedrine in the four groups (table III). However, it is interesting to note that ephedrine was required in 16 of the 34 patients who received their initial injection of local anaesthetic solution in the sitting position, compared with seven of the 30 patients in the lateral position. The maximum reduction in arterial pressure occurred in three patients following the initial injection of local anaesthetic agent. A further two patients complained of dizziness while in the sitting position, despite the absence of hypotension and they were placed immediately in the lateral position. The remainder of the hypotensive episodes occurred in the presence of an extensive extradural block and were associated with transfer of the patient to theatre. The average volume of i.v. fluid which had been infused before the hypotensive episode occurred was 1.42 litre. The mean maximum reduction in arterial pressure in patients who did not receive ephedrine was 17.2 mm Hg, compared with 42.2 mm Hg in those who received ephedrine ($P < 0.05$) (table III).

No infant delivered of a mother meeting Crawford's clinically ideal criteria had an Apgar score of less than 9.

DISCUSSION

In 1984, using a single bolus technique with 0.5 % bupivacaine, Sosis and Ahmad [12] demonstrated a more rapid onset of extradural analgesia. However, there is a wide variation in the doses of local anaesthetic agent required to produce extradural blockade suitable for Caesarean section. More extensive blocks require a greater dose of local anaesthetic agent, but at the expense of a more frequent incidence of hypotension [13]. In addition, peak blood concentrations of local anaesthetic agents have been shown to be significantly greater after a large single bolus than when an incremental technique was used for Caesarean section [14]. Several authors have observed a direct relationship between the patient's height and the spread of local anaesthetic agent in the extradural space [13,15]. Thus a modified incremental technique was chosen, similar to that described by Thorburn and Moir [16] and Dutton and colleagues [1], but relating the first increment to the mother's height. This was chosen arbitrarily on the basis of previous clinical experience and in the belief that, the taller the patient, the larger is the volume of local anaesthetic solution required to produce an effective extradural block for Caesarean section.

This study has shown that the sitting position is not necessary for the development of good sacral block using the large volumes of local anaesthetic agent required for Caesarean section. Indeed, the sitting position appeared to delay the spread of the upper limit of sensory blockade and thus prolonged the time to readiness for surgery. This effect of maternal posture was evident both in patients receiving lignocaine and in those receiving bupivacaine. Patients in the sitting position also required larger doses of the local anaesthetic agent, although this was not statistically significant.

The most satisfactory extradural anaesthesia and the least number of mothers requiring adjuvant drugs were produced by lignocaine with adrenaline 1 in 200000, injected in the lateral position. Judicious use of additional analgesic or anxiolytic agents forms an important part of the successful management of Caesarean section under extradural anaesthesia. Adjuvants are no substitute for an effective extradural block, but in the presence of transient discomfort or anxiety, can improve extradural anaesthesia.

The incidence of hypotension during extradural anaesthesia for Caesarean section varies widely, from 7 % to 44 % [1, 17–19]. By increasing the crystalloid preload from 1 to 2 litre, Lewis and colleagues [17] found that hypotension (20 % reduction in maternal arterial pressure) was reduced from 45 % to 6.5 % without apparent complications. In the present study, 1 litre of crystalloid was infused in the 15 min before injection of the extradural agent and a further 0.5 litre was infused before the maximum reduction in maternal arterial pressure occurred. The 36 % incidence of hypotension in this study differs from that of the previous study by Thorburn and Moir [16], but the two studies are not comparable, as both the initial doses of local anaesthetic agents injected and the i.v. preload differ.

Ephedrine was administered i.v. to hypotensive patients in aliquots of 6 mg. Seven patients receiving bupivacaine required more than one aliquot of ephedrine, compared with three patients who had received lignocaine. Irrespective of the local anaesthetic agent used, ephedrine was required more commonly in patients who had received that initial injection in the sitting position ($P < 0.05$).

It is interesting to note, however, that hypotensive episodes frequently coincided with the final preparations for surgery, for example, urinary catheterization and transfer of the patients to theatre. In the presence of an extensive sympathetic block, movement may cause hypotension. Transient aortocaval compression can occur readily while positioning the patient in the left lateral tilt on the operating table.

There are possibly two further advantages associated with the use of extradural lignocaine. First, there is a substantial body of opinion that lignocaine with adrenaline 1 in 200000 is the solution of choice as an aid to detecting inadvertent i.v. placement of the extradural catheter [20]. Second, intractable cardiovascular toxicity has not been associated with the use of lignocaine, unlike bupivacaine [21, 22]. However, preservative free 2% lignocaine with adrenaline 1 in 200000 is not available in sterile ampoules. The preparation of this solution by the anaesthetist remains a potential source of error, with hazardous consequences should a mistake occur.

REFERENCES

1. Dutton DA, Moir DD, Howie HB, Thorburn J, Watson R. Choice of local anaesthetic drug for extradural Caesarean section. Comparison of 0.5% and 0.75% bupivacaine and 1.5% etidocaine. *British Journal of Anaesthesia* 1984; **56**: 1361–1368.
2. Bromage PR. Spread of analgesic solutions in the epidural space and their site of action: a statistical study. *British Journal of Anaesthesia* 1962; **34**: 161–178.
3. Scanlon JW, Brown U, Weiss JB, Alper MH. Neurobehavioral responses of newborn infants after maternal epidural anesthesia. *Anesthesiology* 1974; **40**: 121–128.
4. Abboud TK, Khoo S, Miller F, Doan T, Henrikson EH. Maternal, fetal and neonatal responses after epidural anesthesia with bupivacaine, 2-chloroprocaine or lidocaine. *Anesthesia and Analgesia* 1982; **61**: 638–644.
5. Abboud TK, Kim KC, Noueihed R, Kuhnert BR, Der Mardirossian N, Moumdjian J, Sarkis F, Nagappala S. Epidural bupivacaine, chloroprocaine or lidocaine for Cesarean section—maternal and neonatal effects. *Anesthesia and Analgesia* 1982; **62**: 914–919.
6. Kuhnert BJ, Harrison MJ, Linn PL, Kuhnert PM. Effects of maternal epidural anesthesia on neonatal behavior. *Anesthesia and Analgesia* 1984; **63**: 301–308.
7. Grundy EM, Rao NL, Winnie AP. Epidural anesthesia and the lateral position. *Anesthesia and Analgesia* 1978; **57**: 95–97.
8. Husemeyer RP, White DC. Lumbar extradural injection pressures in pregnant women. An investigation of relationships between rate of injection, injection pressures and the extent of analgesia. *British Journal of Anaesthesia* 1980; **52**: 55–60.
9. Merry AF, Cross JA, Mayadeo SV, Wild CJ. Posture and the spread of extradural analgesia in labour. *British Journal of Anaesthesia* 1983; **55**: 303–307.
10. Datta S, Alper MH, Ostheimer GW, Brown WU, Weiss JB. Effects of maternal position on epidural anesthesia for Cesarean section, acid–base status and bupivacaine concentration at delivery. *Anesthesiology* 1979; **50**: 205–209.
11. Hodgkinson R, Hussain FJ. Obesity and cephalad spread of analgesia following epidural administration of bupivacaine for Cesarean section. *Anesthesia and Analgesia* 1980; **59**: 89–92.
12. Sosis M, Ahmad I. An efficient technique for performing extradural blockade. *British Journal of Anaesthesia* 1984; **56**: 928–929.
13. Craft JB, Roizen MF, Dao SD, Edward M, Gilman R. A comparison of T4 and T7 dermatomal levels of analgesia for Caesarean section using the lumbar technique. *Canadian Anaesthetists' Society Journal* 1982; **29**: 264–269.
14. Thompson EM, Wilson CM, Moore J, McClean E. Plasma bupivacaine levels associated with extradural anaesthesia for Caesarean section. *Anaesthesia* 1985; **40**: 427–432.
15. Bromage PR. In: Bromage PR, ed. *Epidural Analgesia*. Philadelphia: W. B. Saunders, 1978; 135.
16. Thorburn J, Moir DD. Epidural analgesia for elective Caesarean section. Technique and its assessment. *Anaesthesia* 1980; **35**: 3–6.
17. Lewis M, Thomas P, Wilkes RG. Hypotension during epidural analgesia for Caesarean section. Arterial and central venous pressure changes after acute intravenous loading with two litres of Hartmann's solution. *Anaesthesia* 1983; **38**: 250–253.
18. Rolbin SH, Cole AFD, Hew EM, Pollard A, Virgent S. Prophylactic intramuscular ephedrine before epidural anaesthesia for Caesarean section: efficacy and actions on fetus and newborn. *Canadian Anaesthetists' Society Journal* 1982; **29**: 148–153.
19. Antoine C, Young BK. Fetal lactic acidosis with epidural anesthesia. *American Journal of Obstetrics and Gynecology* 1982; **142**: 55–59.
20. Moore DC, Batra MS. The components of an effective test dose prior to epidural block. *Anesthesiology* 1981; **55**: 693–696.
21. Albright GA. Epinephrine should be used with the therapeutic dose of bupivacaine in obstetrics. *Anesthesiology* 1984; **61**: 217–219.
22. Marx GF. Cardiotoxicity of local anesthetics—the plot thickens. *Anesthesiology* 1984; **60**: 3–5.

Br. J. Anaesth. (1988), **61**, 154–159

BUFFERING CAPACITY OF NORMAL AND INFLAMED TISSUES FOLLOWING THE INJECTION OF LOCAL ANAESTHETIC SOLUTIONS

A. PUNNIA-MOORTHY

SUMMARY

This study has compared the buffering capacity of inflamed skin with that of normal skin, in rats, following the injection of commonly used, relatively acidic local anaesthetic solutions. Inflammation was induced by the intradermal injection of 1% carrageenan 0.1 ml. Local anaesthetic solution (0.05 ml) was injected intradermally into four to six animals in the irritant (inflamed skin) and control (normal skin) groups. Tissue pH changes were measured continuously by a Roche tissue pH electrode for up to a maximum of 180 min. Contrary to the generally accepted view, there was an increase in buffering capacity in inflamed tissues, thus offering no support for the hypothesis that tissue acidity in inflammation is an important factor in the failure of local anaesthetics to act in inflamed tissues.

Failure to achieve satisfactory anaesthesia following the administration of local anaesthetic agents in acutely inflamed tissues is a recognized clinical phenomenon [1]. Several theories have been put forward to account for this finding; tissue acidity has been quoted most frequently and is generally accepted. This is based on animal studies, reported in the early part of this century, that marked tissue acidity occurs during acute inflammation. It is conceivable, that it affects the dissociation of local anaesthetics and renders them less effective [2–4].

Studies of pH in inflammation are few and, moreover, there is no consistency in the findings [5–13] (table I). The results of the most recent study [13] showed only a small reduction of pH in inflammation, the maximum being of the order of 0.5 pH unit. The maximum tissue acidity occurred 6 h following administration of 1% carrageenan and this was more acidic compared with the tissue acidity in *Staphylococcus aureus*-induced inflammation. Such a small change in tissue pH may or may not alter significantly the buffering capacity of inflamed compared with that of normal tissues. This study was designed therefore to evaluate changes in buffering capacity of inflamed tissues following injection of relatively acidic local anaesthetic solutions.

In this study buffering capacity is defined as the time taken by normal and inflamed skin to buffer its pH back to within or near the normal range, following the injection of solutions of varying pH and composition. It is thought that this definition represents a more practical pharmacological means of comparing the buffering capacity of tissues.

TABLE I. *Previous studies of pH in inflammation.* *In vivo *study*

Authors	pH of exudate (range)
Schade, Neukirch and Halpert [5]*	5.98–6.82
Koldajew and Altschuler [6]	5.80–7.20
Menkin [7]	6.60–7.55
Steinberg and Dietz [8]*	6.60–7.22
Spector [9]	7.40–8.30
Edlow and Sheldon [10]	7.00–7.33
Hutchins and Sheldon [11]	7.015–7.380
Hays and Mandell [12]	6.20–7.20
Punnia-Moorthy [13]*	6.87–7.36

A. PUNNIA-MOORTHY, PH.D., F.D.S.R.C.S., F.F.D.R.C.S.I., Joint Department of Oral & Maxillofacial Surgery, Institute of Dental Surgery and University College London Dental School, Mortimer Market, London WC1E 6JD. Present address: Department of Oral Medicine and Oral Surgery, University of Sydney Dental School, 2 Chalmers Street, Surry Hills, N.S.W. 2010, Australia. Accepted for Publication: January 28, 1988.

MATERIALS AND METHODS

Adult female rats of an outbred Wistar strain weighing 200–250 g were used. The animals were fed on special dietary pellets and fresh water *ad libitum*. The irritant used to induce acute inflammation was 0.1 ml of 1% carrageenan (Viscarin 402 (lot 272500) supplied by Marine Colloids Division, Springfield, U.S.A.) in 0.9% sterile saline. This was based on the studies by Di Rosa, Giroud and Willoughby [14], who reported maximal oedema of the rat hind paw, at 4–6 h following injection.

Lignocaine (Xylocaine) 2% plain, 2% lignocaine with adrenaline 1:80000, 2% lignocaine freshly prepared, with 1:80000 adrenaline, and lignocaine vehicle with preservative and without sodium pyrosulphite were used as test solutions.

The electrode used was a miniaturized, combined, glass pH electrode, designed by Roche for the continuous measurement of subcutaneous tissue pH in humans. This electrode has been used extensively in studies of perinatal pH monitoring, to study tissue pH in animals [15] and in critically ill patients [16]. The minimum tissue penetration depth of the electrode is 3 mm, with a distance between the glass tip and the liquid junction of 2 mm and 1 mm, left for obtaining a seal from environmental fluid and air. Temperature dependence of the electrode is negligible at pH 7. At pH 7.4 there is an increase of 0.03 pH units with a temperature variation of 25–37 °C. The response time of the electrode under normal operating conditions is 30 s to 1 min. A Metrohm 605 digital pH meter was used with the electrode and compensation for the effects of temperature on the pH electrode assembly was achieved with a platinum resistance thermometer, placed rectally in the animal and connected to the pH meter. The electrode application kit is illustrated in figure 1. A chart recorder was used to record continuously the tissue pH changes following the injection of local anaesthetic solutions.

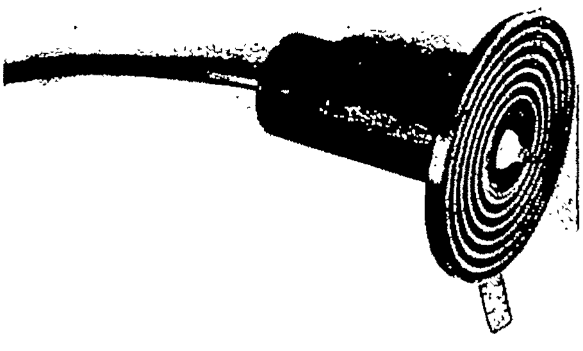


FIG. 1. Roche tissue pH electrode in position in the attachment kit.

The dorsal skin in the midline of the lumbar region was chosen as the experimental site as it was found to be more suitable for the applicaton of the pH electrode (the size of the application kit excluded its use at other sites such as the oral mucosa and the paws).

The animals were allocated to two groups. One group received injections of irritant solution and the other was used as control. The injection of the irritant was performed under ether anaesthesia whilst the injection of the test solutions and subsequent continuous pH measurements were made under anaesthesia from pentobarbitone 40 mg kg^{-1}. An area of skin of approximately 3 × 3 cm in size was shaved and cleaned with 70% alcohol. Each animal in the irritant group received 1% carrageenan 0.1 ml in 0.9% saline injected intradermally at this site. The site of injection was marked with indelible ink by drawing a circle around the weal produced, to facilitate the subsequent injection of local anaesthetic solution into the inflamed skin.

A volume of 0.05 ml of test solutions was chosen, based on the findings of a preliminary study which compared the volume of the solutions injected with the rate of tissue buffering. The test solution was injected intradermally into four to six animals in the irritant and control groups. In the irritant group, test solution was injected at the centre of the inflamed skin, 4–6 h after the injection of carrageenan. As soon as the solution was introduced into the skin, the chart recorder was switched to the "on" position. A stab incision was made in the middle of the weal produced by the injected solution, using a blade held in a specially designed holder which was adjusted so that the depth of the incision remained constant at 3 mm. The scalpel was withdrawn slowly in order to prevent escape of fluid through the wound. Immediately after this the electrode, which had already been placed in the attachment kit, was positioned so that it was inserted completely into the wound. The electrode with its holder was held in place with a double adhesive tape. The time lapse between injection of solutions and the start of pH measurements, that is the time taken for the placement of the electrode in the skin, was approximately 3 min.

Control measurements of skin pH made at sites distant from the experimental area, near the tail end of the animal, used the same standardized technique. Measurements were made at different sites, at the beginning and at the end of each experiment. The pH drift of the electrode was checked at the end of each experiment using calibration buffer solutions and was found to be less than ±0.03 pH units.

The animals were killed by cervical dislocation whilst under anaesthesia, on completion of the experiments.

RESULTS

It was apparent that, when acidic solutions were injected into tissues, considerable time elapsed before the tissue pH was buffered back to within the normal range (tables II–V). The duration was dependent on the pH of the solution injected and its nature (freshly prepared or in cartridge form with an antioxidant) and the presence or the absence of vasoconstrictor (adrenaline).

The maximum reduction in pH and the time taken to reach this level following the injecton of the solution, varied greatly among the solutions investigated. The maximum reduction in pH was much lower for 2% lignocaine with adrenaline 1:80000 (6.82) and freshly prepared lignocaine with adrenaline 1:80000 (6.61), in normal and inflamed skin (tables IV and V). The maximum reduction in pH occurred relatively early for 2% lignocaine with adrenaline 1:80000 and lasted from approximately 30 min until 55 min after injection into normal skin (table IV). In the case of freshly prepared 2% lignocaine with adrenaline 1:80000 the skin pH was reduced to 6.82 at approximately 35 min, after injection into normal skin, and was gradually reduced to 6.61 at 180 min, when the experiment was terminated (table V).

TABLE II. *pH changes (mean$\pm SD/\sqrt{n}$) in normal and inflamed skin of rats following intradermal injection of vehicle solution (pH 4.26)*

Time after injection (min)	pH (normal skin) ($n = 5$)	pH (inflamed skin) ($n = 5$)
3	7.42±0.03	7.35±0.02
5	7.35±0.03	7.27±0.03
10	7.31±0.02	7.24±0.03
15	7.34±0.04	7.25±0.03
20	7.36±0.04	7.28±0.02
25	7.38±0.04	7.30±0.02
30	7.39±0.04	7.31±0.02
35	7.40±0.04	7.32±0.02
40	7.41±0.04	7.33±0.02
45	7.41±0.03	7.33±0.02
50	7.41±0.03	7.33±0.02
55	7.42±0.03	7.33±0.02
60	7.42±0.03	7.33±0.02

TABLE III. *pH changes (mean$\pm SD/\sqrt{n}$) in normal and inflamed skin of rats following intradermal injection of 2% lignocaine plain solution (pH 6.78)*

Time after injection (min)	pH (normal skin) ($n = 5$)	pH (inflamed skin) ($n = 5$)
3	6.85±0.04	7.22±0.03
5	6.84±0.04	7.22±0.04
10	6.88±0.03	7.25±0.06
15	6.93±0.02	7.28±0.06
20	6.97±0.02	7.30±0.05
25	7.01±0.02	7.32±0.04
30	7.05±0.02	7.33±0.04
35	7.08±0.03	7.34±0.03
40	7.11±0.03	7.35±0.03
45	7.13±0.03	7.36±0.02
50	7.15±0.03	7.36±0.01
55	7.17±0.04	7.37±0.02
60	7.18±0.04	7.37±0.02
70	7.20±0.04	
80	7.22±0.04	
90	7.22±0.04	

TABLE IV. *pH changes (mean$\pm SD/\sqrt{n}$) in normal and inflamed skin of rats following intradermal injection of 2% lignocaine with 1:80000 adrenaline (pH 3.23)*

Time after injection (min)	pH (normal skin) ($n = 4$)	pH (inflamed skin) ($n = 4$)
3	7.05±0.10	7.45±0.03
5	6.98±0.07	7.39±0.05
10	6.92±0.03	7.20±0.03
15	6.88±0.01	7.12±0.04
20	6.86±0.01	7.07±0.03
25	6.84±0.02	7.04±0.03
30	6.82±0.03	7.02±0.03
35	6.82±0.04	7.00±0.02
40	6.82±0.04	6.99±0.02
45	6.82±0.05	6.99±0.03
50	6.82±0.05	6.98±0.03
55	6.82±0.05	6.99±0.04
60	6.83±0.06	6.99±0.05
70	6.83±0.06	7.00±0.06
80	6.85±0.06	7.01±0.06
90	6.86±0.06	7.02±0.07
105	6.89±0.06	7.04±0.07
120	6.94±0.05	7.05±0.07
135	6.98±0.04	7.07±0.07
150	7.02±0.04	7.08±0.07
180	7.06±0.02	7.10±0.07

TABLE V. *pH changes (mean ± SD/√n) in normal and inflamed skin of rats following intradermal injection of freshly prepared 2% lignocaine with adrenaline 1:80000 (pH 5.25)*

Time after injection (min)	pH (normal skin) ($n = 5$)	pH (inflamed skin) ($n = 5$)
3	7.17±0.06	7.29±0.06
5	7.11±0.06	7.18±0.06
10	7.02±0.06	7.07±0.07
15	6.96±0.06	6.99±0.08
20	6.91±0.06	6.96±0.07
25	6.88±0.06	6.93±0.07
30	6.85±0.05	6.91±0.07
35	6.82±0.05	6.90±0.08
40	6.80±0.04	6.89±0.08
45	6.78±0.04	6.89±0.08
50	6.76±0.04	6.88±0.08
55	6.75±0.04	6.88±0.09
60	6.73±0.04	6.88±0.09
70	6.71±0.04	6.88±0.10
80	6.68±0.04	6.88±0.11
90	6.66±0.04	6.88±0.11
105	6.64±0.04	6.88±0.12
120	6.62±0.03	6.88±0.13
135	6.61±0.04	6.88±0.13
150	6.61±0.03	6.89±0.13
180	6.61±0.01	6.88±0.10

The main finding was the relative increase in buffering capacity in inflamed skin, as indicated by the increased rate of buffering following the injection of each of the solutions investigated (figs 2–5).

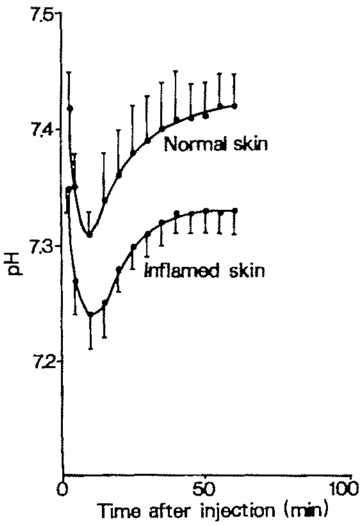


FIG. 2. Comparison of buffering capacity of normal and inflamed skin of rats following intradermal injection of 0.05 ml of vehicle solution (control skin pH: 7.36±0.01).

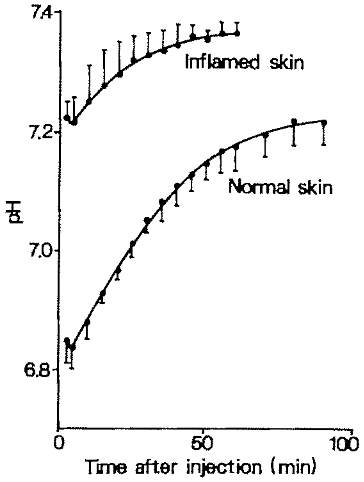


FIG. 3. Comparison of buffering capacity of normal and inflamed skin of rats following intradermal injection of 0.05 ml of 2% lignocaine plain solution (control skin pH: 7.34±0.01).

DISCUSSION

The variation among the solutions tested in maximum reduction in pH and the time taken to reach this level cannot be explained fully. The response time of the electrode which, according to the manufacturer's data may be delayed under worst conditions to 10 min for reaching ±0.01 pH units, could be a factor in determining the time taken to reach the maximum pH reduction whilst

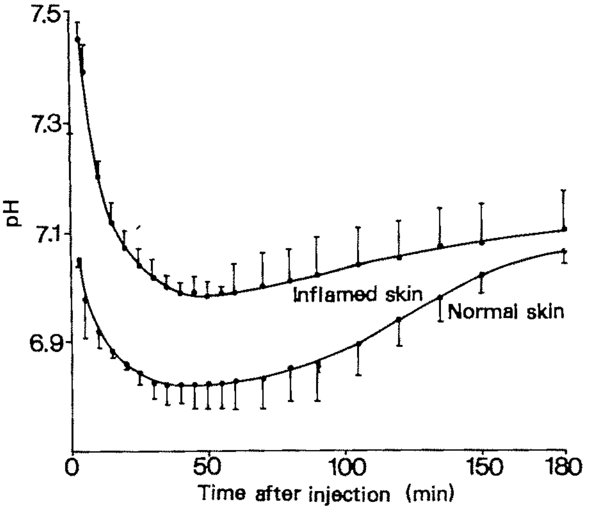


FIG. 4. Comparison of buffering capacity of normal and inflamed skin of rats following intradermal injection of 0.05 ml of 2% lignocaine with adrenaline 1:80000 (control skin pH: 7.28±0.02).

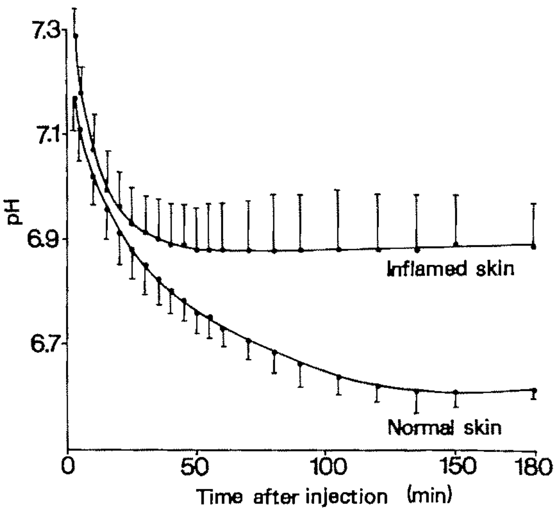


FIG. 5. Comparison of buffering capacity of normal and inflamed skin of rats following intradermal injection of 0.05 ml of freshly prepared 2% lignocaine with adrenaline 1:80000 (control skin pH: 7.34±0.01).

the level of maximum pH reduction could be dependent on the pH of the test solution.

However, the reason for the slow buffering of the relatively more alkaline 2% lignocaine plain solution (pH 6.78) compared with that of the vehicle solution (pH 4.26) is not clear (figs 2, 3). The vehicle solution used in this study was sterile water containing sodium chloride 6.0 mg ml^{-1} and methyl hydroxybenzoate 1.0 mg ml^{-1}. It may be that a small amount (0.05 ml) of such a solution could be buffered almost instantly to the original tissue pH, particularly in the absence of a vasoconstrictor.

A persistent worsening acidosis was found in the case of freshly prepared 2% lignocaine with adrenaline 1:80000 (fig. 5). The only explanation for this is to speculate that freshly prepared adrenaline is relatively more potent than the adrenaline with antioxidant present in the local anaesthetic cartridges.

In the case of vehicle solution, a plateau for pH in inflamed skin was attained marginally more quickly than that in normal skin, but the tissue pH in inflamed skin remained slightly lower (about 0.075 pH unit) at all measurement times (fig. 2). Such a finding may be explained on the basis that there is a small reduction in tissue pH in acute inflammation induced by carrageenan [13].

There are three possible explanations for the increase in the buffering capacity of the inflamed skin observed in this study.

(1) Hyperaemia, stasis and increased vascular permeability in acute inflammation result in increased accumulation of red blood cells and plasma protein at the site of injury, resulting in local increase in the protein buffer system.

(2) Increased vascular permeability, assisted by hyperaemia and stasis in the micro circulation following irritation, would produce exudation in the tissues, resulting in a local increase in extracellular fluid. Dilution of any solution following injection into such a tissue would therefore be expected. The increase in local dilution may explain to a degree the effectiveness of repeated local anaesthetic injections and local anaesthetics of increased strength (5% lignocaine), when used to anaesthetize inflamed teeth in patients [17, 18].

(3) Increase in the rate of absorption of injected local anaesthetic solution in inflamed tissues has been cited as one of the reasons for the failure of nerve block. If this is so, it should be reflected in an increase in buffering capacity following the injection of acidic local anaesthetic solutions as observed in this study.

Measurement of a baseline value (pH of inflamed skin) before injection of test solutions was not possible with the experimental design of this study, as leakage of test solution might have occurred during injection through the wound created for pH measurements. However, induction of inflammation of the skin in rats using 1% carrageenan is a well established technique [14, 19], and in a recent study [13] in which inflammation was induced by 1% carrageenan and the pH was measured by the same electrode as used in the present study, the decrease in tissue pH was found to be of the order of 0.5.

Review of the literature has revealed only a few studies on the buffering of acidic local anaesthetic solutions following injection into normal tissues [20, 21]. The results are similar to those of the present study, in that the time required for neutralization was prolonged, depending on the acidity of the solution and the presence of adrenaline. However, review of the literature has failed to reveal studies of the buffering capacity of inflamed tissues.

In conclusion, the findings of this study offer no support for the hypothesis that tissue acidity is an important factor in the failure of local anaesthetics to produce nerve block in inflamed tissues. Further studies are required to evaluate the role of local dilution and increased rate of absorption in this phenomenon.

ACKNOWLEDGEMENT

I am grateful to Professor D. C. A. Picton for his helpful criticisms during this study.

REFERENCES

1. Roberts DH, Sowray JH. *Local Analgesia in Dentistry*. 2nd edn. Bristol: John Wright, 1979; 60.
2. de Jong RH. *Local Anesthetics*. 2nd edn. Illinois: Charles C. Thomas, 1977; 46.
3. Evers H, Haegerstam G. *Handbook of Dental Local Anaesthesia*. Schultz Medical Information: Denmark, 1981; 194.
4. Bennett CR. *Monheim's Local Anesthesia and Pain Control in Dental Practice*. 7th edn. St Louis: C. V. Mosby, 1984; 131.
5. Schade H, Neukirch P, Halpert A. Über lokale Acidosen des Gewebes and die Methodik ihrer intravitalen Messung, zugleich ein Beitrag zur lehre der Entzündung. *Zeitschrift fur die Gesamte Experimentelle Medizin* 1921; **24**: 11–56.
6. Koldajew B, Altschuler M. Zur Frage über die active Reaktion der Exsudate bei chronischen und akuten Entzündungen. *Zeitschrift fur Immunitatsforschung* 1930; **69**: 18–24.
7. Menkin V. Studies on inflammation. X. The cytological picture of an inflammatory exudate in relation to its hydrogen ion concentration. *American Journal of Pathology* 1934; **10**: 193–210.
8. Steinberg B, Dietz A. Inflammation of serous surfaces. Hydrogen ion concentration in relation to cell type. *Archives of Pathology* 1938; **25**: 777–784.
9. Spector WG. The mediation of altered capillary permeability in acute inflammation. *Journal of Pathology and Bacteriology* 1956; **72**: 367–380.
10. Edlow DW, Sheldon WH. The pH of inflammatory exudates. *Proceedings of the Society for Experimental Biology and Medicine* 1971; **137**: 1328–1332.
11. Hutchins GM, Sheldon WH. pH of inflammatory exudates in granulocytopenic rabbits. *Proceedings of the Society for Experimental Biology and Medicine* 1973; **143**: 1014–1017.
12. Hays RC, Mandell GL. pO_2, pH and redox potential of experimental abscesses. *Proceedings of the Society for Experimental Biology and Medicine* 1974; **147**: 29–30.
13. Punnia-Moorthy A. Evaluation of pH changes in inflammation of the subcutaneous air pouch lining in the rat, induced by carrageenan, dextran and *Staphylococcus aureus*. *Journal of Oral Pathology* 1987; **16**: 36–44.
14. Di Rosa M, Giroud JP, Willoughby DA. Studies of the mediators of the acute inflammatory response induced in rats in different sites by carrageenan and turpentine. *Journal of Pathology* 1971; **104**: 15–29.
15. Hochberg HM, Lauersen NH, George NED, Van Poznak A. Evaluation of continuous monitoring of tissue pH in cats. *American Journal of Obstetrics and Gynecology* 1978; **131**: 770–774.
16. Rithalia SV, Herbert P, Tinker J. Continuous monitoring of tissue pH. *British Medical Journal* 1979; **1**: 1460.
17. Rood JP, Sowray JH. Clinical experience with 5 per cent lignocaine solution. *Journal of Dentistry* 1980; **8**: 128–131.
18. Eldridge DJ, Rood JP. A double-blind trial of 5 per cent lignocaine solution. *British Dental Journal* 1977; **142**: 129–130.
19. Di Rosa M. Biological properties of carrageenan. *Journal of Pharmacy and Pharmacology* 1972; **24**: 89–102.
20. Björn H. The neutralisation of acid local anaesthetic solutions in the tissues. *Svensk Tandläkare-Tidskrift* 1947; **40**: 853–867.
21. Wennberg E, Haljamäe H, Edwall G, Dhuner KG. Effects of commercial (pH:3.5) and freshly prepared (pH:6.5) lidocaine–adrenaline solutions on tissue pH. *Acta Anaesthesiologica Scandinavica* 1982; **26**: 524–527.

Br. J. Anaesth. (1988), **61**, 160–164

EFFECT OF PATIENT-CONTROLLED ANALGESIA ON PLASMA CATECHOLAMINE, CORTISOL AND GLUCOSE CONCENTRATIONS AFTER CHOLECYSTECTOMY

I. W. MØLLER, K. DINESEN, S. SØNDERGÅRD, U. KNIGGE AND H. KEHLET

SUMMARY

To quantify the effects of postoperative pain relief on surgical stress response, 16 patients undergoing cholecystectomy were allocated randomly to double-blind treatment with either fentanyl by patient controlled analgesia (PCA) with the Prominject plus saline given s.c. by nurses on demand (PCA group) or saline by the infusion pump plus morphine 10 mg/70 kg s.c. by nurses on demand (control). Pain intensity (VAS) and plasma catecholamine, cortisol and glucose concentrations were measured 2-hourly for 12 h after operation. PCA improved postoperative pain intensity ($P < 0.05$) and reduced plasma cortisol ($P < 0.05$), but not glucose and catecholamine concentrations compared with the control group. Thus improved postoperative pain relief per se *by PCA with systemic opioids had no major influence on the catabolic response to abdominal surgery.*

Postoperative pain constitutes one of the mechanisms involved in the endocrine-metabolic response to surgery [1].

Pain alleviation by extradural local anaesthetics reduces the stress response, especially during operations on the lower part of the body, while extradural opioids have only a minor effect, despite producing sufficient pain relief [1].

Patient-controlled analgesia (PCA) has been demonstrated to produce good pain relief [2, 3], but its effect on postoperative endocrine-metabolic changes remains unclear.

The purpose of this study was to investigate the influence of postoperative pain relief with PCA on postoperative changes in plasma catecholamine, cortisol and glucose concentrations.

PATIENTS AND METHODS

Sixteen otherwise healthy patients scheduled for elective cholecystectomy with subcostal incision were allocated randomly to postoperative pain treatment with either PCA (group I) or subcutaneous morphine on demand (group II) in a double-blind study. None of the patients was suffering from hormonal disease or receiving any medication. The study was approved by the Ethics Committee of Copenhagen municipal hospitals and written informed consent was obtained from each patient.

The patients were premedicated with oral diazepam 10 mg/70 kg 1–2 h before induction of anaesthesia. All operations began between 8 a.m. and 1 p.m. Anaesthesia was induced with thiopentone and intubation facilitated by suxamethonium 1–1.5 mg kg^{-1}. Anaesthesia was maintained with 0.5–1.5% halothane and 67% nitrous oxide in oxygen using a circle system. Muscle relaxation was achieved with intermittent doses of pancuronium, and incremental doses of fentanyl 0.05 mg were given i.v. not later than 45 min before the end of surgery.

In the recovery room all patients were given subcutaneous morphine 10 mg/70 kg. According to the randomization, group I (eight patients) received a continuous infusion of fentanyl 40.5

IB W. MØLLER*, M.D.; KENN DINESEN, M.D.; SØREN SØNDERGÅRD, M.D.; Department of Anesthesiology, Bispebjerg Hospital, Copenhagen, Denmark. ULRIK KNIGGE, M.D.; HENRIK KEHLET, M.D., PH.D.; Department of Surgical Gastroenterology, Hvidovre Hospital, Hvidovre, Denmark.

Accepted for Publication: January 22, 1988.

*Present address, for correspondence: Department of Anaesthesiology, Herlev Hospital, Herlev Ringvej, 2730 Herlev, Denmark.

μg/50 kg h^{-1} plus boluses of 9 μg/50 kg controlled by the patient via a microprocessor-controlled infusion pump (Prominject, Pharmacia, Uppsala, Sweden). In addition, they received isotonic saline 0.5 ml s.c. on demand. Group II (eight patients) received isotonic saline via the infusion pump and subcutaneous morphine 10 mg/70 kg on demand in a volume equal to that for group I. Both groups received additional morphine 5 mg/70 kg s.c. on request, if pain relief was insufficient.

The patients received isotonic saline 10–15 ml kg^{-1} h^{-1} i.v. during the first 2 h and thereafter 1–2 ml kg^{-1} h^{-1}. Intraoperative bleeding, which never exceeded 500 ml, was corrected by administration of isotonic saline 2.5 ml/ml of blood lost. None of the patients received blood transfusion or sympathomimetic agents.

Venous blood was obtained for measurement of cortisol, glucose, adrenaline and noradrenaline immediately before the first injection of morphine and again 2, 4, 6, 8, 10 and 12 h later.

Pain intensity was estimated using a 10-cm visual analogue scale (VAS) where 0 = no pain and 10 = unbearable pain.

Plasma cortisol concentrations were measured by a commercial radioimmunoassay (Kingo Diagnostics, Haslev, Denmark) and plasma glucose concentration by a routine glucose oxidase method. Plasma adrenaline and noradrenaline concentrations were measured by a radioenzymatic technique [4]. Plasma was mixed with an equal volume of ice-cold perchloric acid 0.6 mol $litre^{-1}$ containing 0.1% EGTA and centrifuged. The supernatant was frozen at −20 °C until required for assay. The sensitivity of the assay was 10–20 pg ml^{-1}. The intra-assay coefficients of variations for noradrenaline and adrenaline were 6.8 and 4.3%, respectively, and the interassay coefficients of variation 14.8 and 12.3%, respectively. The plasma concentrations of noradrenaline and adrenaline in normal resting subjects were 305 ± 101 pg ml^{-1} (mean ± SD) and 87 ± 20 pg ml^{-1} ($n = 15$), respectively.

ECG and heart rate were displayed continuously on an oscilloscope and arterial pressure was monitored intermittently by sphygmomanometry.

Statistical analysis was performed using the Wilcoxon test for intragroup variation and the Mann–Whitney test for intergroup variation. P values less than 0.05 were regarded as significant.

RESULTS

Mean age was lower in group I (56 ± 4 yr *v.* 67 ± 4 yr, $P < 0.05$). Patient weight (group I 66 ± 4 kg, group II 74 ± 4 kg (mean ± SEM)) was similar in the two groups, as was duration of surgery (group I 86 ± 10 min, group II 89 ± 9 min). Mean arterial pressure was not significantly different between the two groups at any stage.

The amounts of fentanyl used during operation (group I 0.14 ± 0.09 mg, group II 0.10 ± 0.06 mg) were not statistically different. The amount of fentanyl used after operation in group I varied from 434 to 1231 μg (mean 819 μg) and only one patient asked for additional morphine (10 mg). In group II the mean dose of morphine received in this period was 13 mg (range 0–40 mg).

The mean pain intensity score was significantly

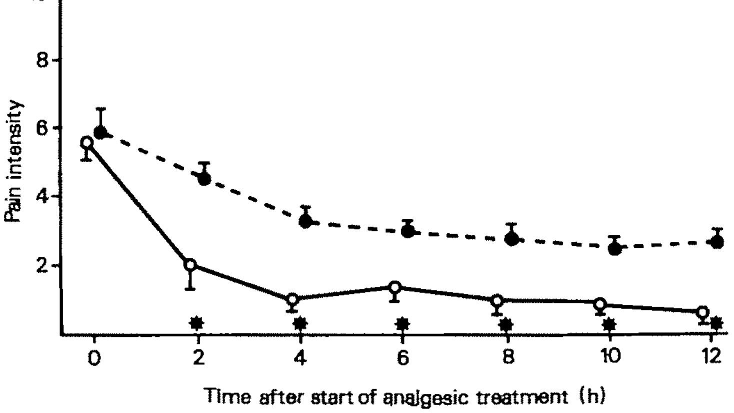


FIG. 1. Pain intensity scores (arbitrary units) (mean ± SEM) after cholecystectomy in patients given PCA with fentanyl (○——○) ($n = 8$) or morphine on request (●- - -●) ($n = 8$). $^{*}P < 0.05$.

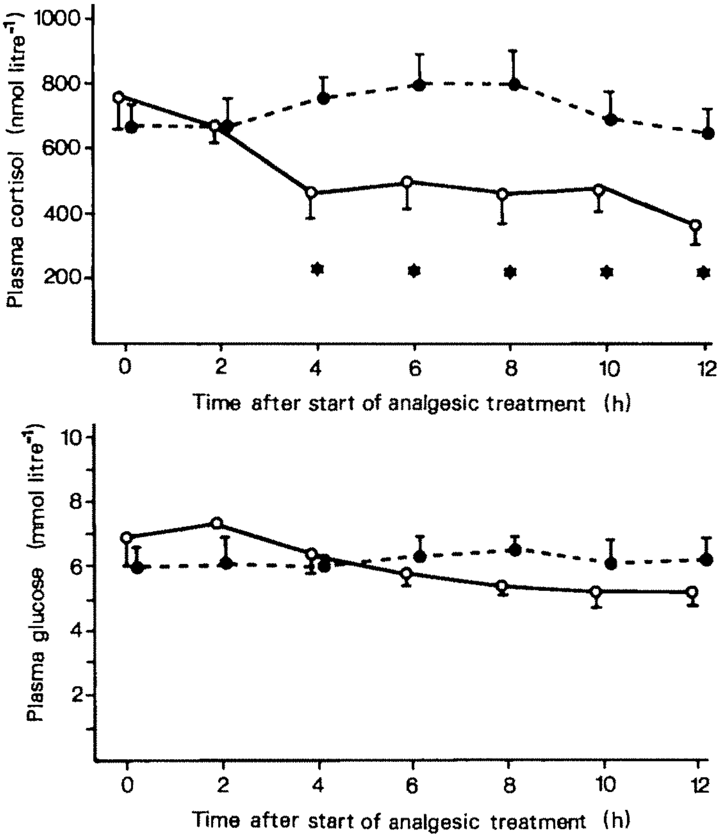


FIG. 2. Changes in plasma cortisol and glucose concentrations (mean ± SEM) after cholecystectomy in patients given PCA with fentanyl (○——○) ($n = 8$) or morphine on request (●---●) ($n = 8$). $^*P < 0.05$.

lower in group I (PCA) from 2 to 12 h after operation (fig. 1).

Plasma cortisol concentrations were identical at the start of analgesic treatment and increased after operation in both groups, but were significantly lower from 4 to 12 h after operation in group I compared with group II (fig. 2). Plasma glucose concentrations were similar in the two groups and remained unchanged throughout the study (fig. 2).

Plasma concentrations of adrenaline were similar and constant in both groups (fig. 3). Plasma noradrenaline concentrations were also constant throughout the study, but those in group I were significantly less than in group II 6 h after operation (fig. 3).

DISCUSSION

The release mechanisms involved in the endocrine metabolic response to surgery are predominantly afferent neurogenic stimuli, although various, mostly unknown humoral substances also contribute [1]. The role of specific pain stimuli in releasing various aspects of the stress response has not been clearly evaluated, but it is well documented that pain *per se*, either during acute experimental pain or in patients with chronic pain, leads to an endocrine metabolic response [1].

The effect of intraoperative systemic administration of opioids on the surgical stress response is well documented [5]. Thus high-dose *intra*-operative opioid anaesthesia inhibits the intra- and initial postoperative endocrine metabolic changes to abdominal surgery [6–8], but this attenuation does not extend into the later postoperative period from 4 to 9 h [9].

Studies on postoperative pain relief with single-dose injection of various opioids have shown either no effect or only slight attenuation of the stress response. Thus buprenorphine 0.3 mg i.m.

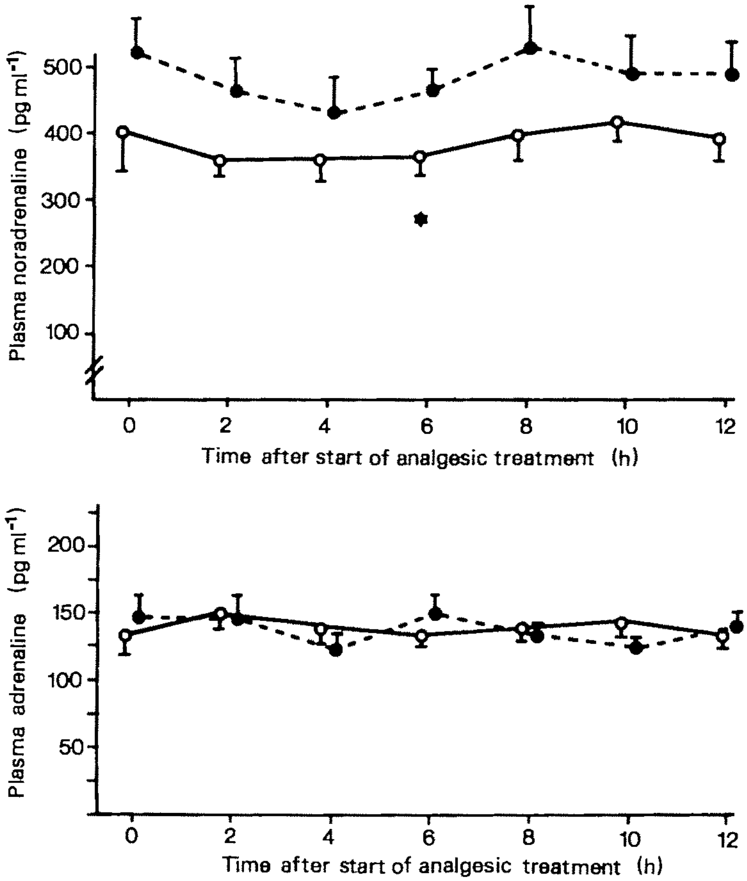


FIG. 3. Changes in plasma adrenaline and noradrenaline concentrations (mean ± SEM) after cholecystectomy in patients given PCA with fentanyl (O——O) ($n = 8$) or morphine on request (●---●) ($n = 8$). *$P < 0.05$.

and i.v. produce only a slight reduction in plasma cortisol and glucose concentrations [10] and meptazinol 100 mg or morphine 15 mg i.m. failed to diminish the stress response [11].

The normal postoperative increase in oxygen consumption was either unaltered [12] or inhibited [13] following pain relief with small doses of morphine and pethidine, respectively. In contrast, a single dose of fentanyl 3.5 μg kg^{-1} administered immediately after operation reduced systemic oxygen uptake and splanchnic release of glucose and 3-hydroxybutyrate [14, 15].

Patient controlled analgesia has been shown to be an effective technique for postoperative pain relief [2, 3, 16], and our results confirm this and have shown, in addition, that PCA with i.v. fentanyl has no major effect on the surgical stress response. Only the plasma cortisol response was affected, and the extent of attenuation was small. These results may not be unexpected, since the dose of morphine necessary to reduce the *intra*-operative stress response is approximately 2–4 mg kg^{-1} and that for fentanyl is 30 μg kg^{-1} [1].

Our results are also consistent with the observations during postoperative pain relief by administration of extradural opioids. Extradural or intrathecal morphine [17–20] or extradural diamorphine [21, 22] had no important effect on various endocrine-metabolic variables despite producing improved pain relief. Furthermore, extradural morphine 4 mg every 12 h for 72 h after abdominal surgery had no effect on urinary excretion of cortisol, adrenaline, noradrenaline and nitrogen, either on separate days or cumulatively over 4 days, neither did pain scores correlate with urinary excretion of stress hormones [23].

Thus all studies using either systemic or extradural administration of opioids in doses applicable to postoperative use in patients breathing spontaneously have demonstrated either no or only a slight effect on the surgical stress response. This is emphasized by the present study, where optimal pain alleviation using PCA with i.v. fentanyl also failed to reduce the stress response to any major extent following cholecystectomy.

REFERENCES

1. Kehlet H. Pain relief and modification of the stress response. In: Cousins MJ, Phillips GD, eds. *Acute Pain Management*. New York, Edinburgh, London, Melbourne: Churchill Livingstone, 1986; 49–75.
2. White WD, Pearce DJ, Norman J. Postoperative analgesia: a comparison of intravenous on-demand fentanyl with epidural bupivacaine. *British Medical Journal* 1979; 2: 166–167.
3. Rosenberg PH, Heino A, Scheinin B. Comparison of intramuscular analgesia, intercostal block, epidural morphine and on-demand i.v.-fentanyl in the control of pain after upper abdominal surgery. *Acta Anaesthesiologica Scandinavica* 1984; **28**: 603–607.
4. Ben-Jonathan N, Porter JC. A sensitive radioenzymatic assay for dopamine, norepinephrine and epinephrine in plasma and tissue. *Endocrinology* 1976; **98**: 1497–1507.
5. Kehlet H. The stress response to anaesthesia and surgery: release mechanisms and modifying factors. *Clinics in Anaesthesiology* 1984; 2: 315–339.
6. Hall GM, Young C, Holdcroft A, Alaghband-Zadeh J. Substrate mobilisation during surgery. *Anaesthesia* 1978; **33**: 924–930.
7. Cooper GM, Paterson JL, Ward ID, Hall GM. Fentanyl and the metabolic response to gastric surgery. *Anaesthesia* 1981; **36**: 667–671.
8. Haxholdt OS, Kehlet H, Dyrberg V. Effect of fentanyl on the cortisol and hyperglycemic response to abdominal surgery. *Acta Anaesthesiologica Scandinavica* 1981; **25**: 434–436.
9. Møller IW, Krantz T, Wandall E, Kehlet H. Effect of alfentanil anaesthesia on the adrenocortical and hyperglycaemic response to abdominal surgery. *British Journal of Anaesthesia* 1985; **57**: 591–594.
10. McQuay HJ, Bullingham RES, Paterson GMC, Moore RA. Clinical effects of buprenorphine during and after operation. *British Journal of Anaesthesia* 1980; **52**: 1013–1019.
11. Kay HN, Allen MC, Bullingham RES, Baldwin D, McQuay RJ, Moore HA, Price RK, Sear JW. Influence of meptazinol on metabolic and hormonal responses following major surgery. *Anaesthesia* 1985; **40**: 223–228.
12. Gelman S, Laws HL, Potzick J, Strong S, Smith L, Erdemir H. Thoracic epidural vs balanced anesthesia in morbid obesity: an intraoperative and postoperative hemodynamic study. *Anesthesia and Analgesia* 1980; **59**: 902–908.
13. Fournell A, Wilhelmy B, Falke K, Sandmann W, Böhmer G. Kontinuerliche messung der sauerstoffaufnahme bei postoperativer periduralanalgesie. In: Wust HJ, Zindler M, eds. *Neue Aspekte in der Regionalanaesthesie*. Berlin: Springer-Verlag, 1980; 54–60.
14. Wiklund L. Splanchnic oxygen uptake in relation to systemic oxygen uptake during postoperative splanchnic blockade and postoperative fentanyl analgesia. *Acta Anaesthesiologica Scandinavica* 1975; **19** (Suppl. 58): 29–40.
15. Wiklund L, Jorfeldt L. Effects of abdominal surgery under general anaesthesia and of postoperative analgesic therapy on splanchnic exchange of some blood borne energy metabolites. *Acta Anaesthesiologica Scandinavica* 1975; **19** (Suppl. 58): 41–58.
16. Bennett RL, Batenhorst RL, Bivins BA, Bell RM, Graves DA, Foster TS, Wright BD, Griffen WO. Patient-controlled analgesia. *Annals of Surgery* 1982; **195**: 700–705.
17. Christensen P, Brandt MR, Rem J, Kehlet H. Influence of extradural morphine on the adrenocortical and hyperglycaemic response to surgery. *British Journal of Anaesthesia* 1982; **54**: 23–27.
18. Jørgensen BC, Andersen HB, Engquist A. Influence of epidural morphine on postoperative pain, endocrine-metabolic, and renal responses to surgery. A controlled study. *Acta Anaesthesiologica Scandinavica* 1982; **26**: 63–68.
19. Rutberg H, Håkanson E, Anderberg B, Jorfeldt L, Mårtensson J, Schildt B. Effects of the extradural administration of morphine, or bupivacaine, on the endocrine response to upper abdominal surgery. *British Journal of Anaesthesia* 1984; **56**: 233–238.
20. Downing R, Davis I, Black J, Windsor CWO. Effect of intrathecal morphine on the adrenocortical and hyperglycaemic responses to upper abdominal surgery. *British Journal of Anaesthesia* 1986; **58**: 858–861.
21. Cowen MJ, Bullingham RES, Paterson GMC, McQuay HJ, Turner M, Allen MC, Moore A. A controlled comparison of the effects of extradural diamorphine and bupivacaine on plasma glucose and plasma cortisol in postoperative patients. *Anesthesia and Analgesia* 1982; **61**: 15–18.
22. Normandale JP, Schmulian C, Paterson JL, Burrin J, Morgan M, Hall GM. Epidural diamorphine and the metabolic response to upper abdominal surgery. *Anaesthesia* 1985; **40**: 748–753.
23. Hjortsø N-C, Christensen NJ, Andersen T, Kehlet H. Effects of the extradural administration of local anaesthetic agents and morphine on the urinary excretion of cortisol, catecholamines and nitrogen following abdominal surgery. *British Journal of Anaesthesia* 1985; **57**: 400–406.

Br. J. Anaesth. (1988), **61**, 165–168

NO EFFECT OF CONTINUOUS I.P. INFUSION OF BUPIVACAINE ON POSTOPERATIVE ANALGESIA, PULMONARY FUNCTION AND THE STRESS RESPONSE TO SURGERY

N. B. SCOTT, T. MOGENSEN, A. GREULICH, N. C. HJORTSØ AND H. KEHLET

SUMMARY

In a double-blind prospective study, 20 patients undergoing major abdominal surgery were allocated randomly to receive a continuous 8-h i.p. infusion of either physiological saline or 0.25% bupivacaine 20 ml h^{-1} (in saline) following a loading dose of saline 1 ml kg^{-1} or 0.25% bupivacaine 1 ml kg^{-1} on entering the peritoneum. The following variables were measured before and at 2-h intervals during the infusion: serum glucose and cortisol concentrations, forced vital capacity, forced expiratory volume in the first second, peak expiratory flow rate and pain at rest, on mobilization and on coughing (visual analogue scale). Postoperative pain, impairment in pulmonary function and increase in serum cortisol and glucose concentrations were not influenced by the i.p. infusion of bupivacaine when compared with saline. This study shows that the i.p. instillation of therapeutically safe doses of bupivacaine was without effect in the management of pain, postoperative pulmonary dysfunction and the stress response in this group of patients.

Few clinicians would accept that analgesia in the postoperative period is adequate and that, at present, any regimen affords complete analgesia in every patient for any given situation. In addition, it may be argued that the hormonal response to surgical trauma is largely undesirable, resulting in erosion of body mass and tissue reserve, thus leading to an increase in surgical morbidity [1]. It is not possible to block this response following upper abdominal and thoracic procedures, and only extradural blockade is able to do so in the case of lower abdominal procedures [1, 2]. Thus the development, in these areas, of new ideas and techniques relevant to clinical practice is to be encouraged.

The concept of instilling local anaesthetic into the peritoneum is not new, lignocaine and bupivacaine having been used with or without sedation for outpatient laparoscopy [3–6]. A recent study showed that a *single* intraoperative dose of bupivacaine reduced the period of postoperative colonic inhibition, and it was suggested that such a method may reduce the incidence of adynamic ileus. Furthermore, the authors noted a significant reduction in the hyperglycaemic stress response with i.p. bupivacaine, lasting for 4–8 h after the bolus dose [7]. The purpose of this study was to evaluate the effect of a continuous i.p. infusion of bupivacaine on analgesic requirements, pulmonary function and the stress response following major abdominal surgery.

PATIENTS AND METHODS

Twenty patients were entered into a randomized double-blind controlled trial, having given informed consent. They were divided into two groups, for upper or lower abdominal procedures. An upper abdominal procedure was defined as one with a supraumbilical incision and in which the affected viscera derived their nerve supply

---

N. B. SCOTT, F.R.C.S.(ED.), H. KEHLET, M.D., PH.D. (Department of Surgical Gastroenterology); T. MOGENSEN, M.D., ANNE GREULICH, M.D., N. C. HJORTSØ, M.D. (Department of Anaesthesia); Hvidovre University Hospital, DK-2650 Hvidovre, Copenhagen, Denmark. Accepted for Publication: October 21, 1987.

Correspondence to H. K.

from the coeliac plexus. Patients in each group were then randomly allocated to receive either i.p. saline or bupivacaine.

On the day before surgery, forced vital capacity (FVC), forced expiratory volume (FEV_1) and peak expiratory flow rate (PEFR) were obtained using a Vitalograph spirometer (Birmingham, U.K.), along with assessment of pain using a visual analogue scale (VAS) at rest, on coughing and on mobilization. Blood samples were taken immediately before operation and serum cortisol (radioimmunoassay, Kingo Diagnostics, Haslev, Denmark) and glucose (routine glucose oxidase method) concentrations measured.

Patients were given diazepam 0.3 mg kg^{-1} for premedication. Anaesthesia was induced with thiopentone 2–5 mg kg^{-1} and intubation of the trachea facilitated with suxamethonium 1.5 mg kg^{-1} following precurarization with pancuronium 0.01 mg kg^{-1}. Maintenance of anaesthesia was with 67% nitrous oxide in oxygen and 0.5–1% halothane; supplements of pancuronium and fentanyl were given, if required. The bupivacaine group received fentanyl 0.26 ± 0.04 mg and the saline group fentanyl 0.31 ± 0.07 mg (mean ± SEM) ($P > 0.3$). Neuromuscular blockade was antagonized with neostigmine 2.5–5 mg (plus atropine 1–2 mg). Surgery was performed in a conventional manner. However, a small opening was made before the peritoneum was entered, and a wide bore tube inserted. Either 0.25% bupivacaine 1 mg kg^{-1} or physiological saline 1 ml kg^{-1} was instilled, diluted in a further 300 ml of physiological saline to ensure adequate spread of the solution. The patient was then gently tilted in all directions for 5 min, after which surgery continued in a routine manner. The surgeons were instructed to remove only fluid which hindered visualization of the operating field.

Before closure of the wound, an extradural catheter (Portex) was placed in the peritoneal space through a puncture wound several centimetres from the incision. For upper abdominal procedures the catheter was positioned beneath the right crus of the diaphragm, while for procedures in the lower abdomen it was positioned beneath the bifurcation of the aorta. The catheter was not fixed in position. An intraperitoneal infusion of 20 ml h^{-1} of either 0.25% bupivacaine or physiological saline was commenced on completion of surgery. If analgesia was insufficient, systemic morphine was given on request of the patient.

The preoperative indices were reassessed at 2, 4, 6 and 8 h following the commencement of the infusion. On cessation of the infusion the catheter was removed.

ECG was recorded throughout the study in all patients.

Statistics

Differences between the two groups for clinical data, VAS and pulmonary function were calculated using a Mann–Whitney test for unpaired observations. Cortisol and glucose concentrations in the two groups were compared using an unpaired *t* test.

TABLE I. *Clinical data*

	Saline i.p.	Bupivacaine i.p.
Age (yr) (mean (SEM))	62 (3–7)	53 (4–1)
M/F	2/8	2/8
Procedure (upper/lower)	5:5	5:5
Duration of surgery (min) (SEM)	206 (22)	172 (19)
8-h postop. morphine requirements (mg) (mean (SEM))	10.4 (1.4)	16.4 (2.4)

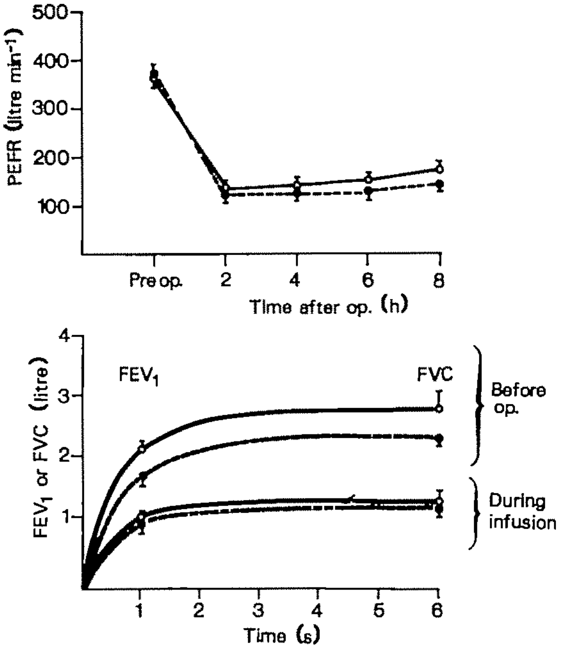


FIG. 1. Mean (±SEM) values for PEFR, and FVC and FEV_1 before and during the continuous intraperitoneal infusion of bupivacaine (○——○) *v.* saline (●---●). $n = 10$ each category.

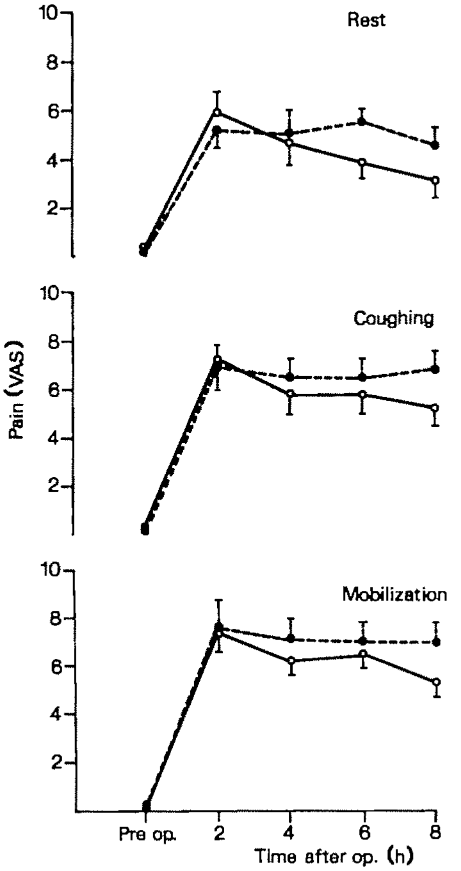


FIG. 2. Mean pain scores at rest, on coughing and on mobilization before and during the continuous i.p. infusion of bupivacaine (O——O) v. saline (●---●). $n = 10$ each category.

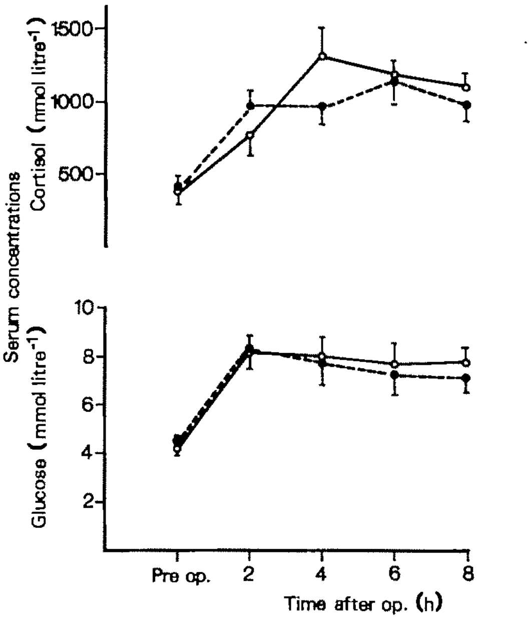


FIG. 3. Mean serum cortisol and serum glucose concentrations before and during the continuous i.p. infusion of bupivacaine (O——O) v. saline (●---●). $n = 10$ each category.

RESULTS

Table I documents the clinical data of the patients and the operations performed; there were no differences between the two groups for age, sex, or duration and site of surgery.

There were no differences in pulmonary function between the two groups at any period during the infusion: FEV_1, FVC and PEFR were all reduced to about 60% of their preoperative values (fig. 1). Pain scores were unacceptably high throughout the study period if a score of less than 4 is regarded as acceptable (fig. 2). There was a trend towards a reduction in pain score and a decrease in analgesic requirement in the bupivacaine group, but this was neither statistically nor clinically significant. Mean total morphine dose in the 8-h period was 10.4 mg in the bupivacaine group (range 3–15 mg) and 16.4 mg in the saline group (range 5–50 mg). There were increases in serum cortisol and glucose concentrations in both groups following surgery, with no differences between the two groups (fig. 3). There was no evidence of central nervous system or cardiovascular toxicity with bupivacaine in any patient.

DISCUSSION

Current knowledge pertaining to visceral afferent neural pathways and the contribution to these of free nerve endings in the peritoneum is poor. It is believed, however, that both in some way contribute to the mechanisms underlying the neuroendocrine response to surgical stress, and that they may also be involved with postoperative lung dysfunction. Since both of these events are maximal following thoracic and upper abdominal procedures, and since no currently available method can prevent them in this situation, the instillation of local anaesthetic into the peritoneal cavity is theoretically attractive.

Local anaesthetics have been instilled into the intraperitoneal cavity either as a sole technique or in combination with sedation for laparoscopy and tubal ligation [3–6]. The technique is said to be well tolerated by patients, but no detailed assessment of pain was made in these studies. Serum concentrations following a single administration of 0.5% bupivacaine 20 ml (100 mg) were well below those which promote cardiac and central nervous system toxicity, suggesting that larger doses could be safely administered [4]. Therefore, we felt that a high dose regimen might provide adequate analgesia after major abdominal surgery.

However, the continuous administration of a large therapeutic dose of bupivacaine (2.5 mg kg^{-1}), plus 0.25% bupivacaine 20 ml h^{-1} in the early postoperative period, has conferred no benefit on any of the measured indices. At the same time analgesia was very poor, highlighting the fact that somatic wound pain probably is the most important peripheral component of postoperative pain.

Our metabolic results are at variance with those obtained by Rimbäck and colleagues [7]. However, their study combined single-dose i.p. bupivacaine 2 mg kg^{-1} in 300 ml of isotonic saline with single-dose intercostal blocks from T8 to T12 using 0.5% bupivacaine 20 ml at the end of surgery and is, therefore, not directly comparable with the present study. We know of no data regarding the metabolic response to trauma following intercostal blockade alone, but such a combination, by also relieving somatic pain, might conceivably be responsible for the findings of Rimbäck and colleagues [7] since, as we have shown, the use of i.p. bupivacaine by itself is not.

In conclusion, the continuous i.p. infusion of bupivacaine following surgery in clinically safe doses confers no benefit over morphine as required on pulmonary function, pain or the stress response to trauma.

REFERENCES

1. Kehlet H. Stress free anaesthesia and surgery. *Acta Anaesthesiologica Scandinavica* 1979; **23**: 503–504.
2. Kehlet H. The stress response to anaesthesia and surgery: Release mechanisms and modifying factors. *Clinical Anaesthesiology* 1984; **2**: 315–339.
3. Jefferson Penfield A. Laparoscopic sterilisation under local anesthesia. *American Journal of Obstetrics and Gynecology* 1974; **119**: 733–736.
4. Spielman FJ, Hulka JF, Ostheimer GW, Mueller RA. Pharmacokinetics and pharmacodynamics of local analgesia for laparoscopic tubal ligations. *American Journal of Obstetrics and Gynecology* 1983; **146**: 821–824.
5. Brown DR, Fishburne JI, Robertson VO, Hulka JF. Ventilatory and blood gas changes during laparoscopy with local anesthesia. *American Journal of Obstetrics and Gynecology* 1976; **124**: 741–745.
6. Deeb RJ, Viechjnicki MB. Laparoscopic tubal ligation under peritoneal lavage anaesthesia. *Regional Anaesthesie* 1985; **10**: 24–27.
7. Rimbäck G, Cassuto J, Faxen A, Högström S, Wallin P, Tollesson PO. Effect of intraabdominal bupivacaine instillation on postoperative colonic motility. *Gut* 1986; **27**: 170–175.

Br. J. Anaesth. (1988), **61**, 169–172

INTERCOSTAL NERVE BLOCKADE PRODUCING ANALGESIA AFTER APPENDICECTOMY

P. BUNTING AND J. F. McGEACHIE

Appendicectomy is the commonest emergency abdominal operation. One in six of the U.K. population is affected [1], the maximum incidence being in the third decade [2]. On the first day after surgery, opioid analgesics are usually required and are prescribed most often as on-demand i.m. injections.

Intercostal nerve blockade (ICNB) may provide good analgesia of long duration following upper abdominal surgery [3, 4] and urological procedures with loin incisions [5]. There is no published report on the use of ICNB after operations to the lower abdomen. The most commonly used incisions used for uncomplicated appendicectomy are within the dermatomes supplied by the 10th, 11th and 12th thoracic nerves on the right [7]. It should therefore be possible to provide analgesia following appendicectomy using ICNB.

PATIENTS AND METHOD

The study was approved by the local Ethics Committee and informed consent was obtained from patients or their guardians.

Patients were studied if the proposed incision was the gridiron, Lanz, or a modification of these. Patients excluded were those younger than the age of 14 yr, the obese (where palpation of the ribs would be difficult, or a paramedian incision was to be used to facilitate surgical access) and those with a history of previous psychiatric illness. Before induction of anaesthesia, the patients were allocated randomly to one of two groups, the control group or the ICNB group.

SUMMARY

Intercostal nerve blockade of the 10th, 11th and 12th thoracic nerves on the right side was compared with i.m. papaveretum as analgesia after appendicectomy. Patients with intercostal nerve blockade had significantly less pain at 0, 4, 8 and 12 h after operation and required less papaveretum (mean 0.26 mg kg^{-1}/24 h) compared with the controls (mean 0.62 mg kg^{-1}/24 h). There were no complications in either group. Intercostal nerve blockade may provide better quality analgesia following appendicectomy than i.m. papaveretum alone.

Anaesthesia was standardized. Following preoxygenation for a minimum of 3 min, anaesthesia was induced with thiopentone 4–5 mg kg^{-1}. Cricoid pressure was applied and suxamethonium 1–1.5 mg kg^{-1} was administered to facilitate intubation of the trachea. After there were signs of recovery from suxamethonium, vecuronium 0.1 mg kg^{-1} was given. All patients received fentanyl 1 μg kg^{-1}. Ventilation was controlled using intermittent positive pressure ventilation. Anaesthesia was maintained with halothane 0.5–1 % and 67 % nitrous oxide in oxygen.

After induction of anaesthesia, patients in the ICNB group were turned onto their left side and 3 ml of 0.25 % bupivacaine with adrenaline 1 in 200 000 was injected into the subcostal groove of each of the 10th, 11th and 12th ribs on the right. The technique used was that described by Moore [8–10] at the angle of the rib using a 3.5-cm 23-gauge needle.

At the end of surgery, residual neuromuscular blockade was antagonized with neostigmine 50 μg kg^{-1} and atropine 25 μg kg^{-1}. On the return of adequate spontaneous respiration the patients were turned onto their left side and the trachea

---

PETER BUNTING*, M.B., CH.B., F.F.A.R.C.S.; JOHN F. McGEACHIE, M.B., CH.B., F.F.A.R.C.S.; Oldham Royal Infirmary, Union Street West, Oldham OL8 1DJ. Accepted for Publication: December 18, 1987.

*Present address, for correspondence: Department of Anaesthesia, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL.

extubated before the patients were transferred to the recovery area.

Both groups of patients were prescribed papaveretum in a dose of approximately 0.25 mg kg^{-1}. The papaveretum was given by the ward nursing staff at their discretion should the patients request analgesia. The ward nursing staff were not aware of the group to which patients had been allocated.

Following recovery from anaesthesia, heart rate and arterial pressure were recorded and the intensity of any pain was assessed. Assessment of pain was made by the patients using a scale of 0–10 where 0 = no pain at all, and 10 = most pain [11]. This method of pain scoring was used because it was found to be learnt more easily by the patient than the linear analogue scale and required no hand–eye co-ordination, which we had found to be poor in some patients during the early phase of recovery.

Observations were recorded at 0, 4, 8, 12, 18 and 24 h after surgery. In addition, the time of administration of the first dose of papaveretum, the total number of doses and the total dose of papaveretum given during the 24-h study period were noted.

The presence of peritonitis, defined as either the presence of free fluid in the peritoneal cavity, or inflammation spreading to either parietal peritoneum or onto the bowel wall surrounding the appendix with or without inflammatory exudates, was recorded. The duration of stay in hospital was also noted.

The results obtained were analysed using the Mann–Whitney *U* test to determine statistical significance. A value of $P \leqslant 0.05$ was considered significant.

RESULTS

Thirty patients (ASA I or II) were studied, 15 in each group. There were no significant differences between patient characteristics of the two groups (table I).

Pain scores at 0, 4, 8 and 12 h were significantly different (fig. 1, table II). The patients in the control group had higher scores, although the severity of their pain became less during this time. At 18 h and 24 h after surgery there were no significant differences in the pain scores between the two groups.

In the control group there were two patients with local peritonitis and both of these patients reported pain scores in the mid range. In the ICNB group there were five patients with peritonitis; three reported low to mid range pain scores and the other two patients reported the highest pain scores and received more injections of papaveretum, with the first dose administered before all the other patients in the ICNB group.

TABLE I. *Demographic data (mean ± SEM (range))*

	Control group	ICNB group
Sex (F/M)	9/6	9/6
Age (yr)	22.7 ± 9.0 (15–39)	26.3 ± 11.6 (14–50)
Weight (kg)	64.7 ± 7.7 (51–80)	60.9 ± 11.1 (40–75)

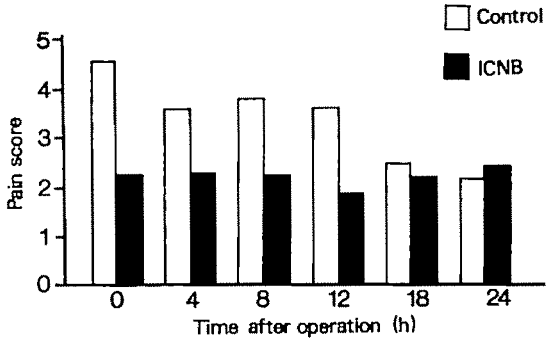


FIG. 1. Mean pain scores.

TABLE II. *Pain scores (mean values (range))*

	Time (h)					
	0	4	8	12	18	24
Control group	4.5 (1–9)	3.5 (1–9)	3.7 (0–9)	3.5 (0–7)	2.5 (1–6)	2.1 (0–7)
ICNB group	2.3 (0–10)	2.3 (0–6)	2.2 (0–6)	1.9 (0–6)	2.2 (0–6)	2.4 (0–6)
P	<0.01	<0.05	<0.05	<0.05	ns	ns

The time from the end of operation to the first dose of papaveretum is shown in figure 2. In the first 2 h after surgery, eight patients in the control group received papaveretum while no patient in the ICNB group required analgesia. After 4 h a total of 11 patients in the control group needed papaveretum, but only the two patients described above had needed postoperative analgesia in the ICNB group. Six hours after operation, 14 patients in the control group and seven in the ICNB group had received papaveretum. By 8 h all patients in the control group had received

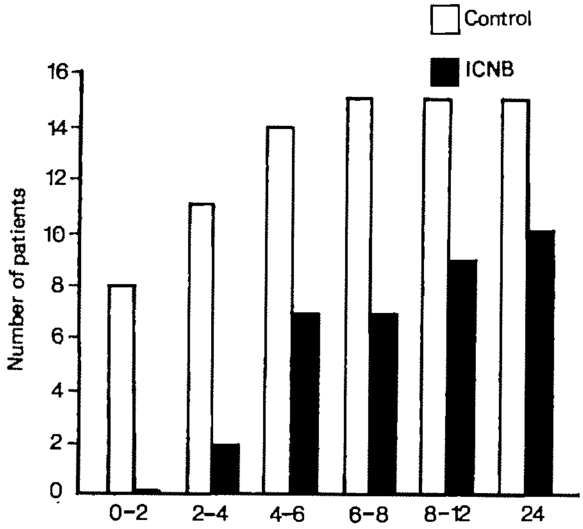


FIG. 2. Time from the end of surgery to the first dose of papaveretum.

TABLE III. *Mean and range total dose of papaveretum administered in the 24 h following surgery.* *P < 0.01

	Mean dose (mg kg^{-1}/24 h)	Range
Control group	0.62	0.17–1.23
ICNB group	0.26*	0–0.86

analgesia, whereas in the ICNB group a total of only 10 patients had needed papaveretum, seven within the first 6 h and three more in the following 10 h.

The number of doses of papaveretum given to both groups was significantly different. Thirty-one injections of papaveretum were administered to the control group and 16 doses were administered to the ICNB group ($P = <0.05$). The total dose of papaveretum that was administered to the control group in the first 24 h was 0.62 mg kg^{-1} (range 0.17–1.23) compared with 0.26 mg kg^{-1} (range 0–0.86) in the ICNB group ($P = <0.05$) (table III).

Throughout the observation period heart rate and arterial pressure remained within normal limits for all patients in both groups, with no significant differences between them.

The mean hospital stay in the control group was 3.4 days (range 3–5 days) and that in the ICNB 3.7 days (range 2–10 days). With the exception of one patient in the study group, who had a pyrexia for which no cause was found, the hospital stay was not significantly different between the groups.

DISCUSSION

After appendicectomy, pain is severe during the first 24 h and opioid analgesics may be required. They are given usually i.m. on request from the patient. This regimen of pain relief is one of the least effective methods of providing postoperative analgesia [12].

It might be expected that patients receiving the largest doses of papaveretum would report the lowest pain scores. In this study, patients with ICNB reported lower pain scores, but received a smaller total dose of papaveretum than control patients. This reflects a better quality of analgesia provided by ICNB when compared with i.m. papaveretum. Analgesia proved to be of long duration following a single ICNB at the time of operation. Patients in the control group required their first dose of papaveretum sooner after the completion of surgery than did the ICNB group. Five patients in the ICNB group required no papaveretum in the postoperative period.

However, two patients obtained no relief of pain from the ICNB. Both these patients had local peritonitis which was noted at the time of surgery. It is possible that the failure of the ICNB to provide analgesia in these patients may have resulted from inflammation spreading to involve areas of peritoneum innervated by nerves other than thoracic nerves 10, 11 and 12 on the right. Pain sensation from inflammation of either small or large bowel is transmitted to the spinal cord through the splanchnic sympathetic nerves. However, the most likely possibility is that the ICNB had failed. If this were so, our success rate of 87% is similar to that in other series of ICNB. For example, Mulroy [13] reported 56 of 70 blocks placed at the angle of the rib produced analgesia to pinprick in the corresponding dermatome: a success rate of 80%.

In our series, there were no complications from the ICNB. The commonest complications of ICNB are intravascular injection and pneumothorax [14]. Pneumothorax should be rare when blocking the three lowest thoracic nerves, because the injections are made below the reflections of the visceral pleura [6]. An accidental intravascular injection of the local anaesthetic, even if all the injection (bupivacaine 7.5 mg) were to be given intravascularly, is unlikely to be significant clinically [15].

In conclusion we have shown that ICNB of the 10th, 11th and 12th thoracic nerves on the right provides good analgesia after appendicectomy.

REFERENCES

1. Ellis H, Calne RY. *Lecture Notes In General Surgery*. 5th edn. London, Edinburgh, Melbourne: Blackwell Scientific Publishers, 1979; 206.
2. Bailey H, Love M. In: Rains AJH, Ritchie HD, eds. *A Short Practice of Surgery*. 18th edn. London: Lewis HK, 1984; 987.
3. Nunn JF, Slavin G. Posterior intercostal nerve block for pain relief after cholecystectomy. Anatomical basis and efficacy. *British Journal of Anaesthesia* 1980; 52: 253–260.
4. Cronin KD, Davies MJ. Intercostal nerve block for postoperative pain relief. *Anesthesia and Intensive Care* 1976; 4: 259–261.
5. Noller DW, Gillenwater JY, Howards SS, Vaughan ED. Intercostal nerve block with flank incision. *Journal of Urology* 1977; **117**: 759–761.
6. Warwick R, Williams PL, eds. *Gray's Anatomy*. 35th edn. London: Longman, 1062–1064.
7. Farquarson EL. *Textbook of Operative Surgery*. 6th edn. London: Churchill Livingstone, 1978; 618.
8. Moore DC. *Regional Block*. 4th edn. Illinois: Charles & Thomas, 1976; 163–166.
9. Moore DC, Bush WH, Scurlock JE. Intercostal nerve block. A Roentgenographic anatomic study of technique and absorption in humans. *Anesthesia and Analgesia* 1980; **59**, 815–825.
10. Moore DC. Intercostal nerve block: spread of India ink injected to the ribs costal groove. *British Journal of Anaesthesia* 1981; **53**: 325–329.
11. Downie WW, Leatham PA, Rhind VM, Wright V, Branco JA, Anderson JA. Studies with pain rating scales. *Annals of the Rheumatic Diseases* 1978; **37**: 378–381.
12. Rutter PC, Murphy F, Dudley HAF. Morphine-controlled trial of different methods of administration for postoperative pain relief. *British Medical Journal* 1980; **280**: 12–13.
13. Mulroy MF. Intercostal Block At the Midaxillary Line. Abstracts, Annual Meeting American Society for Regional Anaesthesia. *Regional Anaesthesia* 1985; 10: 1–39.
14. Moore DC. Intercostal block for postoperative somatic pain following surgery of thorax and upper abdomen. *British Journal of Anaesthesia* 1975; **47**: 284–286.
15. Moore DC, Batra MS. The components of an effective test dose prior to epidural block. *Anesthesiology* 1981; **55**: 693–696.

Br. J. Anaesth. (1988), **61**, 173–179

PHARMACODYNAMICS OF ALFENTANIL AS A SUPPLEMENT TO NITROUS OXIDE ANAESTHESIA IN THE ELDERLY PATIENT

H. J. M. LEMMENS, A. G. L. BURM, J. G. BOVILL AND
P. J. HENNIS

SUMMARY

The pharmacodynamics of alfentanil given as a supplement to nitrous oxide anaesthesia were studied in 10 elderly patients undergoing lower abdominal surgery. Plasma alfentanil concentration–effect curves for perioperative stimuli and for the probability of needing naloxone at the end of surgery were fitted by logistic regression. The concentration at which the probability of no response was 0.5 (Cp_{50}) for laryngoscopy was 356 ng ml^{-1}, for opening the peritoneum 295 ng ml^{-1} and for closing the peritoneum 254 ng ml^{-1}. The average Cp_{50} for the intra-abdominal part of the operation was 268±97 ng ml^{-1}. The Cp_{50} for needing naloxone was 174 ng ml^{-1}. These findings are similar to published values for young healthy females undergoing lower abdominal surgery. Our findings suggest that the pharmacodynamics of alfentanil in the elderly are similar to those in younger adults.

The proportion of elderly subjects in the population is increasing; consequently, the number of elderly patients presenting for surgery will also increase. Perioperative mortality in this group of patients is higher than for other age groups [1]. In the elderly patient in particular, an anaesthetic technique should be used which provides stable anaesthesia, avoids overdose of drugs and allows rapid recovery. In addition, better knowledge of the pharmacology of anaesthetic drugs in the elderly will improve management and decrease perioperative mortality and morbidity. To achieve this, knowledge of the physiological changes which may affect the pharmacokinetics and pharmacodynamics of drugs used in anaesthesia is necessary.

Alfentanil is a synthetic opioid with a rapid onset and a short duration of action. The rapid onset of action is related to rapid blood–brain equilibration [2], the short duration to rapid (re)distribution and a short elimination half-life [3, 4]. A comparative study by Helmers and colleagues [5] on the pharmacokinetics of alfentanil in elderly and young patients demonstrated that the plasma clearance was decreased and the elimination half-life prolonged in the elderly. In a study by Scott and Stanski [6], the elimination half-life of alfentanil was shown to increase significantly with increasing age; clearance did not decrease. Scott and Stanski [6] also studied the effects of age on the pharmacodynamics of alfentanil, using the EEG as a measure of effect. They demonstrated that the alfentanil plasma concentration producing 50% of the maximal spectral edge shift in the EEG (IC_{50}) decreased with increasing age. This suggests that elderly patients are more sensitive to the central nervous effects of alfentanil than are younger patients. However, no data are available on the effects of age on the relationship between alfentanil plasma concentration and response to stimuli during anaesthesia and surgery.

We have studied the pharmacodynamics of alfentanil, given as a supplement to nitrous oxide anaesthesia in the elderly patient, using clinical criteria (probability of suppressing responses to perioperative stimuli) as a measure of effect.

H. J. M. LEMMENS, M.D.; A. G. L. BURM, PH.D.; J. G. BOVILL, M.D., PH.D., F.F.A.R.C.S.I.; P. J. HENNIS, M.D., PH.D.; Department of Anaesthesiology, University Hospital, Rijnsburgerweg 10, 2333 AA Leiden, The Netherlands. Accepted for Publication: November 12, 1987.

Correspondence to H. J. M. L.

TABLE I. *Details of patients studied*

Patient No.	Sex	Age (yr)	Wt (kg)	Condition requiring treatment	Operation
1	M	72	62	Diverticulitis of sigmoid colon	Sigmoid resection
2	M	65	79	Colon carcinoma	Hemicolectomy
3	F	71	59	Ovarian carcinoma	Pelvic clearance
4	F	80	45	Sigmoid carcinoma	Sigmoid resection
5	F	68	75	Uterine prolapse	Hysterectomy
6	M	66	84	Diverticulitis of sigmoid colon	Sigmoid resection
7	F	76	64	Sigmoid volvulus	Sigmoid resection
8	M	65	76	Sigmoid carcinoma	Sigmoid resection
9	F	66	54	Colon carcinoma	Hemicolectomy
10	F	74	77	Uterus carcinoma	Hysterectomy

PATIENTS AND METHODS

Ten patients (aged 65–80 yr, ASA II or III) undergoing lower abdominal surgery were studied. Patients taking antihypertensive drugs or other drugs known to influence the cardiovascular system were excluded. All patients had normal hepatic and renal function, and none had a history of severe cardiac disease. The study was approved by the University of Leiden Medical Ethics Committee and all patients gave informed consent. Details of the patients and of the operative procedures are given in table I.

A computer controlled infusion delivery system (TIAC: Titration of Intravenous Agents by Computer; Janssen Scientific Instruments, Janssen Pharmaceutica, Belgium) was used to administer alfentanil. This system, which was supplied with published pharmacokinetic data from elderly patients [5], allowed a target plasma concentration of alfentanil to be attained rapidly and maintained. In addition, the plasma concentration could be altered rapidly by the anaesthetist. For example, if the target plasma concentration was increased, the new set point was theoretically achieved within 6 s. Thus by increasing or decreasing the target concentration, the anaesthetist could titrate the plasma concentration to the patient's requirements.

Premedication was with temazepam 10 mg by mouth 1 h before surgery and atropine 0.25 mg i.m. 0.5 h before surgery. In the operating theatre ECG electrodes were placed, and a 20-gauge cannula was placed in a radial artery for continuous measurement of arterial pressure and collection of blood samples. Before the induction of anaesthesia, 0.9 % sodium chloride 300–500 ml was infused. Pancuronium 0.02 mg kg^{-1} was given to prevent muscle rigidity, and the patients were preoxygenated. After 3 min, the fresh gas flow was changed from 100 % oxygen to 66 % nitrous oxide in oxygen. Simultaneously, an infusion of alfentanil was started. The target alfentanil plasma concentration for induction of anaesthesia was 475 ng ml^{-1}, to be achieved in 2 min. This choice was based on a previous plasma concentration–effect study in young adults [7]. When consciousness was lost, suxamethonium 1 mg kg^{-1} was given, the trachea intubated and the lungs ventilated with 66 % nitrous oxide in oxygen. Ventilation was adjusted to maintain the end-tidal carbon dioxide concentration between 4 and 5 vol %. After intubation the target alfentanil plasma concentration was decreased to 250 ng ml^{-1}. A 16-gauge cannula was inserted to the right internal jugular vein for measurement of central venous pressure, and the bladder was catheterized. Between 7 and 12 min after intubation of the trachea, laryngoscopy was performed again and a nasogastric tube inserted under direct vision.

If, during surgery, the patient exhibited signs of inadequate anaesthesia, the target alfentanil plasma concentration was increased by 50–100 ng ml^{-1}. If necessary, this was repeated every 5 min. Inadequate anaesthesia was defined by the following criteria:

(1) Increase in systolic pressure by more than 15 mm Hg above normal for that patient. Normal was defined as the lowest pressure measured in the time from admission to hospital until just before premedication.

(2) A heart rate greater than 90 beat min^{-1} in the absence of hypovolaemia.

(3) Other autonomic signs such as sweating, flushing or lachrymation.

(4) Somatic responses such as movement, swallowing, coughing, grimacing or eye movement.

If a patient did not respond during a 15-min period the target plasma concentration was decreased by 50 or 100 ng ml^{-1}. After closure of the peritoneum this period was decreased to 5 min.

To facilitate the identification of somatic responses, pancuronium was given in the minimal dose necessary for surgery. Neuromuscular blockade was monitored using the train-of-four method, by percutaneous stimulation of the facial nerve (Myotest: Odense, Denmark). To avoid hypovolaemia, fluid balance was evaluated at least every 15 min and maintained positive. In addition, central venous pressure was maintained greater than 8 mm Hg. I.v. fluids consisted of 0.9% sodium chloride and, when indicated, either colloids or whole blood.

At the end of surgery nitrous oxide was discontinued, and residual neuromuscular blockade was antagonized, if necessary, with neostigmine 1 mg (given with atropine 0.5 mg). The trachea was extubated once the patient had regained consciousness and when adequate ventilation was established (frequency >10 b.p.m.; end-tidal carbon dioxide concentration <6.5 vol%; tidal volume >7 ml kg^{-1}). If ventilation was inadequate 10 min after the discontinuation of nitrous oxide, naloxone 0.04 mg was given and, when necessary, repeated every 3 min until adequate ventilation occurred without verbal encouragement. In the recovery room naloxone 0.04 mg was given when the rate of ventilation decreased to less than 8 b.p.m.

Arterial blood samples (for the determination of alfentanil plasma concentrations) were collected before the induction of anaesthesia, before laryngoscopy, before skin incision, before opening of the peritoneum and after closure of the peritoneum and skin. Additional samples were taken before any change of the target alfentanil plasma concentration and 4 and 15 min after a stable plasma concentration was achieved. In patients in whom there was spontaneous recovery of ventilation, a blood sample was taken immediately before extubation. In the remaining patients the sample was taken 10 min after the discontinuation of the nitrous oxide, but before the administration of naloxone.

Plasma concentrations of alfentanil were determined by capillary gas chromatography. The coefficient of variation did not exceed 5% in the concentration range concerned.

Data analysis

Using the criteria for inadequate anaesthesia described above, the patient's responses were classified as present or absent. In addition, the plasma alfentanil concentration at that moment was recorded. The presence or absence of a response (or the need for naloxone), and the corresponding plasma concentration were entered in a logistic regression computer program (ELSFIT, [8]) which fitted the data to the following equation:

$$\text{probability of no response} = \frac{Cp^{\gamma}}{Cp_{50}{}^{\gamma} + Cp^{\gamma}}$$

where Cp is the measured plasma alfentanil concentration, Cp_{50} is the concentration at which the probability of no response is 0.5 and γ is a dimensionless index indicating the slope of the response curve. The log-likelihood is used as a measure of the goodness of fit.

Cp_{50} values for specific stimuli, for example laryngoscopy, skin incision, opening and closure of the peritoneum, closure of the skin, and the probability of needing naloxone at the end of the operation were calculated for the group. Individual Cp_{50} values for surgical stimulation during the intra-abdominal part of the surgery were determined for each patient.

Results are expressed as mean ± standard deviation, except for the times for return of heart rate and arterial pressure to normal values after increasing the plasma alfentanil concentration. These times were not normally distributed and are presented as median and range. An unpaired *t* test was used to test the significance of differences in plasma alfentanil concentration between patients requiring and not requiring naloxone. $P < 0.05$ was considered statistically significant.

RESULTS

All patients lost consciousness within 2 min of the start of the alfentanil infusion. No patient responded to laryngoscopy and intubation of the trachea. However, induction of anaesthesia was associated with several side-effects. Despite pretreatment with pancuronium, four patients developed muscular rigidity. In one of these patients it was impossible to ventilate the lungs until suxamethonium had been given. A decrease in systolic arterial pressure greater than 15 mm Hg occurred in five patients during induction, but

TABLE II. *Cp_{50}, γ and log-likelihood for specific stimuli in the group*

Stimulus	Cp_{50} (ng ml^{-1})	γ	Log-likelihood
Laryngoscopy	356	5.0	−5.7
Opening of the peritoneum	295	4.1	−5.9
Closure of the peritoneum	254	8.5	−4.8

TABLE III. *Cp_{50}, γ and log-likelihood for the intra-abdominal part of surgery for individual patients*

Patient No.	Cp_{50} (ng ml^{-1})	γ	Log-likelihood
1	470	3.8	−13.6
2	319	7.2	−5.5
3	230	3.9	−4.1
4	255	4.3	−6.2
5	295	12.4	−5.9
6	269	6.8	−6.7
7	92	7.4	−5.5
8	275	2.0	−11.3
9	289	10.4	−4.5
10	194	3.0	−4.2

TABLE IV. *Type and number of responses to perioperative stimuli*

Response	*n*
Systolic arterial pressure >normal + 15 mm Hg	31
Heart rate >90 beat min^{-1}	12
Somatic responses	10
Other responses	4

before intubation. In two of these patients systolic arterial pressure decreased to 60 and 80 mm Hg, respectively. Arterial pressure was restored to normal after the administration of ephedrine 7.5 mg i.v. and the rapid infusion of 200–300 ml of 0.9 % sodium chloride.

The average duration of anaesthesia was 161 ± 41 min. The total dose of alfentanil given was 24.9 ± 10.8 mg. A response to the fourth stimulus of the train-of-four was detectable for 54 ± 11 % of the duration of anaesthesia. When questioned on the day after surgery, no patient had any recall of events during anaesthesia or surgery.

The calculated Cp_{50} values for the second laryngoscopy, and opening and closure of the peritoneum are shown in table II. Because of a low incidence of responses to intubation of the trachea ($n = 0$), skin incision ($n = 1$) and skin closure ($n = 2$), it was impossible to calculate Cp_{50} for these stimuli. The average measured plasma concentration at intubation was 688 ± 122 ng ml^{-1}. In the patient who responded to skin incision, the alfentanil plasma concentration was 284 ng ml^{-1}. In the other patients the alfentanil plasma concentration ranged from 210 to 385 ng ml^{-1}. In the two patients who responded to skin closure, the alfentanil plasma concentrations were 230 and 261 ng ml^{-1}. In the other patients the alfentanil plasma concentration ranged from 68 to 338 ng ml^{-1}. The Cp_{50} values for the intra-abdominal part of the surgery for each patient are shown in table III. The corresponding plasma concentration *v.* probability curves are shown in figure 1.

The type and the number of responses observed during the study are given in table IV. All responses were rapidly controlled by increasing the target plasma concentration. Systolic arterial pressure returned to normal within 1–9 min (median 2 min). Heart rate returned to normal within 1–8 min (median 2 min).

The relationship between the alfentanil plasma concentration and the probability of needing naloxone is shown in figure 2. The tracheal tube was removed 12 ± 8 min after stopping the nitrous oxide. Six patients needed naloxone (average dose 0.05 ± 0.05 mg) to restore adequate spontaneous ventilation. The measured alfentanil plasma concentration before the administration of naloxone in these patients was 226 ± 50 ng ml^{-1}. The corresponding concentration at the time of extubation in the patients not requiring naloxone was 163 ± 72 ng ml^{-1}. This difference was not significant ($P = 0.13$). Two patients who received naloxone before extubation needed additional naloxone during the recovery period. The first patient was given additional naloxone at 12 and 30 min after extubation, the second 10 min after extubation.

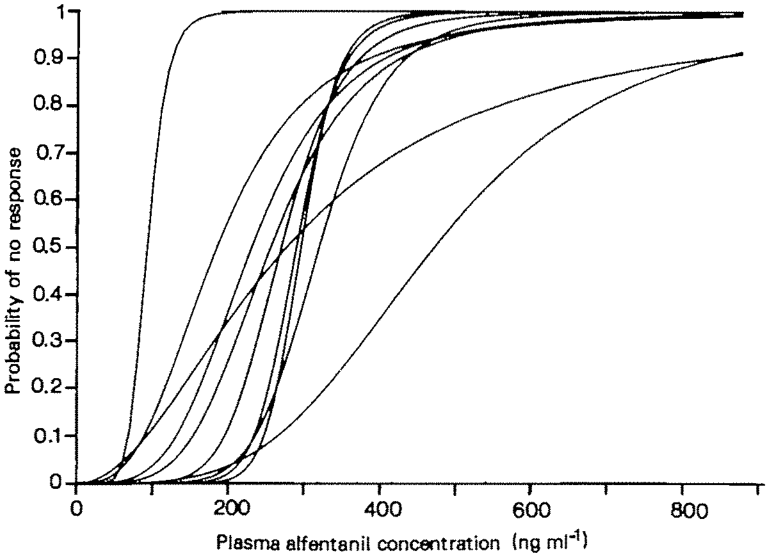


FIG. 1. Alfentanil plasma concentration *v.* effect curves for 10 elderly patients during the intra-abdominal part of lower abdominal surgery.

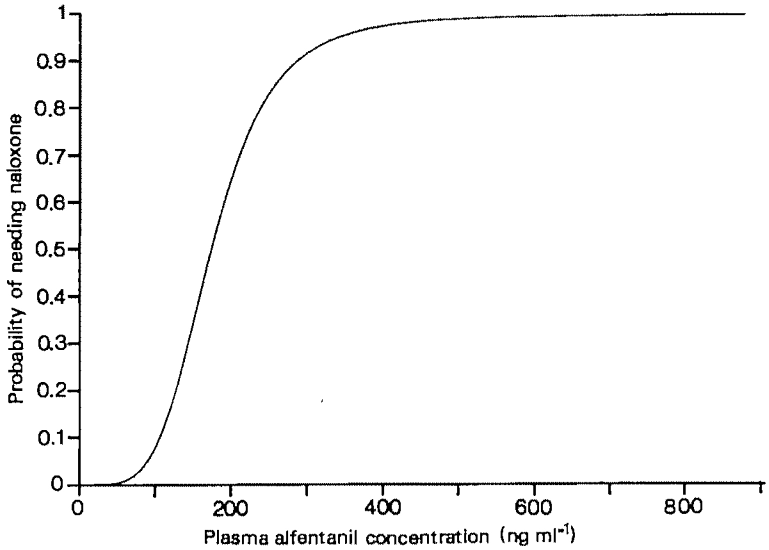


FIG. 2. Relationship between the alfentanil plasma concentration and the probability of needing naloxone at the end of the operation for 10 elderly patients. $Cp_{50} = 174$ ng ml^{-1}; $\gamma = 4.4$; log-likelihood $= -5.6$.

DISCUSSION

Pharmacodynamic studies in which plasma concentrations are not maintained at a steady state are complicated by hysteresis; that is, a time lag between plasma concentration and effect. In this study concentration–response relationships were determined as far as was possible after allowing time for equilibration between plasma and brain concentration. The hysteresis effect with alfentanil ($T_{\frac{1}{2}}K_{e0} = 0.9 \pm 0.3$ min) is significantly less than with fentanyl ($T_{\frac{1}{2}}K_{e0} = 4.7 \pm 1.5$ min), without age dependent changes [6]. Scott and Stanski [6] evaluated the rate of blood–brain equilibration using the EEG. It is likely that their data are also valid for other effect parameters such as signs of light anaesthesia. It is to be expected that brain concentrations will have reached equilibrium within approximately 3–4 K_{e0} half-lives after a stable plasma concentration has been attained; that is, within approximately 4 min in the case of alfentanil. Thereafter, the plasma concentration can be expected to reflect the concentration of alfentanil at the receptor site. Some responses occurred during periods of changing plasma concentrations—after decreasing the target alfentanil plasma concentration, and at the end of surgery when plasma concentrations were declining.

Whereas the target plasma concentration for the induction of anaesthesia was 475 ng ml^{-1}, the actual measured concentration at the time of intubation was 688 ± 122 ng ml^{-1}. This relatively large discrepancy probably results from inadequate characterization of the pharmacokinetics during the initial distribution phase. In this study the computer-controlled infusion system was supplied with pharmacokinetic data from elderly patients [5], based on a two-compartment model. In comparison with a three-compartment model [9], a two-compartment model usually underestimates the initial plasma concentrations, both after administration of a bolus injection and during infusion.

The slope of the plasma alfentanil concentration–response curves was steep ($\gamma > 3$) in most of our patients. For plasma concentrations of alfentanil lying within the linear portion of the response curve, small changes in plasma concentration will, therefore, produce marked changes in effect. When a response occurred during the intra-abdominal part of surgery, this was rapidly abolished by a small increase in the target plasma concentration.

We observed considerable interpatient variability in Cp_{50} (92–470 ng ml^{-1}) calculated for the intra-abdominal part of the procedure. This variability may reflect an inherent variability between patients in the response to alfentanil. However, other factors, including different types of surgery, different surgeons and the underlying disease state may also affect Cp_{50}. In this study, the variability in Cp_{50} did not depend upon the type of surgery. Cp_{50} values in patients undergoing resection of the sigmoid colon (92–470 ng ml^{-1}) were not systematically different from those in patients undergoing other types of surgery (230–390 ng ml^{-1}). The relatively wide range in Cp_{50} may be related to differences between patients in the protein binding of alfentanil. It is generally assumed that the pharmacological effect of drugs is related to the free (unbound) concentration of the drug in plasma, rather than to the total plasma concentration. Therefore, differences in the degree of protein binding may cause variability in the total plasma concentration–effect relationship; that is, Cp_{50}. This variability will be most marked for drugs such as alfentanil which are highly protein bound. The major protein for binding alfentanil is alpha-1-acid glycoprotein [10]. Both malignancy and chronic inflammation, present in most of the patients in this study (table I), increase the serum concentration of alpha-1-acid glycoprotein. Less variability in the Cp_{50} for alfentanil was found in young healthy female patients undergoing gynaecological surgery, in whom less variability in alpha-1-acid glycoprotein concentrations would be expected [7].

The average Cp_{50} for the intra-abdominal part of the surgery in our study (268 ± 97 ng ml^{-1}) was similar to the value of 309 ± 44 ng ml^{-1} reported by Ausems, Hug and Stanski [7] (two-sample t test: $P > 0.10$). The Cp_{50} values for specific stimuli in our elderly patients are also similar to those reported by these authors. In our study, the Cp_{50} for laryngoscopy was 356 ng ml^{-1} and for the probability of needing naloxone 174 ng ml^{-1}. In the study of Ausems, Hug and Stanski [7] the corresponding Cp_{50} values were 475 ng ml^{-1} and 223 ng ml^{-1}.

Thus despite differences in age and disease state, our results are comparable to those of Ausems, Hug and Stanski [7]. This suggests that the pharmacodynamics of alfentanil in elderly patients for perioperative stimuli are similar to those in younger patients. This is in contrast to the finding of Scott and Stanski [6], who used the shift of the spectral edge in the EEG as a measure of pharmacodynamic response.

ACKNOWLEDGEMENTS

This study was supported by Janssen Pharmaceutica, Beerse, Belgium. The authors thank Mrs M. P. R. R. Gladines, Mrs A. E. Muller-de Ruiter and Mr A. A. Vletter for their assistance with the laboratory investigations and Miss M. P. M. Toelen for typing the manuscript.

REFERENCES

1. Farrow SC, Fowkes FGR, Lunn JN, Robertson IB, Samuel P. Epidemiology in anaesthesia. II. Factors affecting mortality in hospital. *British Journal of Anaesthesia* 1982; 54: 811–817.

2. Scott JC, Ponganis KV, Stanski DR. EEG Quantitation of narcotic effect: The comparative pharmacodynamics of fentanyl and alfentanil. *Anesthesiology* 1985; **62**: 234–241.
3. Bovill JG, Sebel PS, Blackburn CL, Heykants J. The pharmacokinetics of alfentanil (R 39209): A new opioid analgesic. *Anesthesiology* 1982; **57**: 439–443.
4. Camu F, Gepts E, Ruquoi M, Heykants J. Pharmacokinetics of alfentanil in man. *Anesthesia and Analgesia* 1982; **61**: 657–661.
5. Helmers JH, van Peer H, Woestenborghs R, Noorduin H, Heykants J. Alfentanil kinetics in the elderly. *Clinical Pharmacology and Therapeutics* 1984; **36**: 239–243.
6. Scott JC, Stanski DR. Decreased fentanyl and alfentanil dose requirements with increasing age. A simultaneous pharmacokinetic and pharmacodynamic evaluation. *Journal of Pharmacology and Experimental Therapeutics* 1987; **240**: 159–166.
7. Ausems ME, Hug CC jr, Stanski DR, Burm AGL. Plasma concentrations of alfentanil required to supplement nitrous oxide anesthesia for general surgery. *Anesthesiology* 1986; **65**: 362–373.
8. Sheiner LB. ELSFIT, a program for the extended least square fit of individual pharmacokinetic data. *Technical Report*, Division of Clinical Pharmacology, University of California, San Francisco, 1981.
9. Maitre PO, Vozeh S, Heykants J, Thomson DA, Stanski DR. Population pharmacokinetics of alfentanil: The average dose–plasma concentration relationship and interindividual variability in patients. *Anesthesiology* 1987; **66**: 3–12.
10. Meuldermans WEG, Hurkmans RMA, Heykants JJP. Plasma protein binding and distribution of fentanyl, sufentanil, alfentanil and lofentanil in blood. *Archives Internationales de Pharmacodynamie et de Thérapie* 1982; **257**: 4–19.

Br. J. Anaesth. (1988), **61**, 180–185

COMPARISON OF LARGE DOSE OF VECURONIUM WITH PANCURONIUM FOR PROLONGED NEUROMUSCULAR BLOCKADE

K. RØRVIK, P. HUSBY, L. GRAMSTAD, J. S. VAMNES,
L. BITSCH-LARSEN AND M.-E. KOLLER

SUMMARY

Dose–duration relationships for vecuronium were determined and the duration of action produced by vecuronium 0.3 mg kg^{-1} shown to equal that of pancuronium 0.1 mg kg^{-1}. Using these doses, the neuromuscular blocking properties and cardiovascular effects of the two drugs were compared. With large dose administration of vecuronium (0.3 mg kg^{-1}), both the onset time (mean 81 s) and the 25–75% recovery index (mean 13.9 min) were about one-half those associated with pancuronium (means 168.5 s and 29.3 min, respectively). The duration of action until 25% recovery was similar with both drugs. There was no evidence of cardiovascular instability with the large dose of vecuronium. Heart rate, however, was significantly slower (range 89.7–94.2% of control) 2–20 min after the injection of vecuronium. Vecuronium 0.3 mg kg^{-1} may have more favourable neuromuscular blocking effects than pancuronium 0.1 mg kg^{-1} and may be preferable to pancuronium when prolonged neuromuscular blockade is required.

Vecuronium has been reported to be without adverse cardiovascular effects, even after the administration of doses as large as 0.3 mg kg^{-1} [1]. Thus by using different doses of this intermediate acting drug, flexibility in its clinical use might be achieved. The purpose of this study was to determine the dose of vecuronium which was necessary to produce a duration of action similar to that of a standard dose of pancuronium (0.1 mg kg^{-1}). Subsequently, these doses of vecuronium and pancuronium were compared with regard to onset time, duration of action, rate of recovery and cardiovascular effects.

PATIENTS AND METHODS

Patients (ASA class I, age 18–60 yr) undergoing elective surgery under general anaesthesia were studied. Signed informed consent was obtained and the study was approved by the hospital Ethics Committee. Haemoglobin concentration, haematocrit and serum concentrations of ASAT, ALAT, ALP, creatinine, calcium and magnesium were determined. Only patients with normal biochemical indices were included in the study. Exclusion criteria were pregnancy, puerperium, medication interfering with neuromuscular function, neuromuscular disorders and body weight deviating by more than 20% from normal.

All patients received diazepam 10 mg by mouth about 1 h before the induction of anaesthesia. In the operating theatre a catheter was inserted into a vein on the back of one hand and connected to a continuous infusion of Ringer's lactate solution. Atropine 0.6 mg, diazepam 10 mg and fentanyl 0.2 mg were given i.v. before needle electrodes were placed s.c. near the ulnar nerve at the wrist, using the arm without the i.v. cannula. Supramaximal stimuli of 0.2 ms duration at a frequency of 0.1 Hz were delivered from a Myotest nerve stimulator (Biometer, Denmark). The force of adduction of the thumb was measured by using a TD-100 transducer (Biometer, Denmark) and

---

K. RØRVIK, M.D.; P. HUSBY, M.D., PH.D.; J. S. VAMNES, M.D.; M.-E. KOLLER, M.D., PH.D.; L. BITSCH-LARSEN, M.D.; Department of Anaesthesiology, N-5016 Haukeland sykehus, University of Bergen, Norway. L. GRAMSTAD, M.D., Department of Anaesthesiology, Rikshospitalet, University of Oslo, Oslo 1, Norway. Accepted for Publication: February 24, 1987.

Correspondence to K. R.

recorded by a Myograph 2000 (Biometer, Denmark). The resting thumb tension was maintained between 200 and 300 g during recordings. Heart rate, systolic, diastolic and mean arterial pressure were recorded with an oscillotonometer (Criticon Dinamap Adult/Pediatric vital signs monitor, Criticon Inc., Florida, U.S.A.). Once a stable twitch response had been obtained, anaesthesia was induced with thiopentone 5 mg kg^{-1} and fentanyl 0.2 mg. Ventilation was assisted via a face mask: 70% nitrous oxide in oxygen was used. Increments of fentanyl were given, as required, during the procedure.

Three minutes after induction of anaesthesia with thiopentone the neuromuscular blocking agent was injected as a single dose over 2–3 s into a fast running infusion of Ringer's lactate solution. Five minutes later the trachea was intubated and mechanical ventilation was instituted (end-tidal carbon dioxide concentration between 4 and 5 vol% (Datex Normocap, Datex, Sweden)). Heart rate and arterial pressure were recorded 3, 2 and 1 min before the injection of the neuromuscular blocking drug.

Onset time was defined as the period from the end of the injection of the neuromuscular blocking drug until the single twitch was depressed to 5% of the control value. Duration of action was defined as the period from the end of the injection until the single twitch response had recovered to 25% of the control value. Recovery index was the time interval from 25% to 75% recovery of single twitch. Neuromuscular function was allowed to recover spontaneously.

The study consisted of two consecutive parts. In part I, 56 patients were selected randomly for study. Sixteen patients received pancuronium 0.1 mg kg^{-1}. Forty patients were divided into five groups receiving vecuronium 0.10, 0.15, 0.20, 0.25 or 0.30 mg kg^{-1}. Onset time and duration of neuromuscular blockade were recorded. Dose–duration curves were constructed and used to estimate the dose of vecuronium producing a duration of action equal to that of pancuronium 0.1 mg kg^{-1}. In part II, 20 patients were allocated to receive, on a random basis, either pancuronium 0.1 mg kg^{-1} or vecuronium 0.3 mg kg^{-1}. The onset time, duration of action and the 25–75% recovery index were recorded. Heart rate and arterial pressure were measured before and 2, 4, 10, 15 and 20 min after the injection of the neuromuscular blocking agent. This part of the study was double-blind.

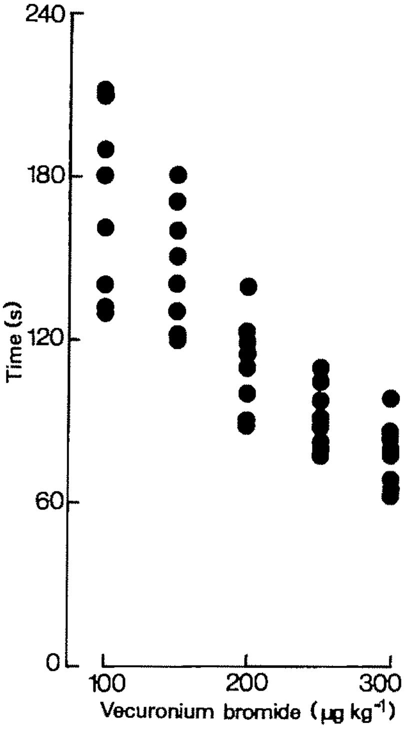


FIG. 1. Effect of increasing doses of vecuronium on the onset of neuromuscular blockade. Experimental conditions as described in the Patients and Methods section.

TABLE I. *Onset time and duration of neuromuscular blocking actions of pancuronium and vecuronium (mean ± SEM)*

Dose (mg kg^{-1})	*n*	Onset time (s)	Duration (min)
Pancuronium			
0.1	16	214.4±21.1	87.4±5.3
Vecuronium			
0.10	8	168.8±11.9	27.6±1.7
0.15	8	146.3±8.1	41.4±2.3
0.20	8	110.0±6.3	55.2±3.1
0.25	8	92.1±5.6	70.4±4.7
0.30	8	76.9±4.5	86.1±3.1

Statistical analysis

A linear regression line was used to estimate the vecuronium dose which produced a duration of action equal to that of pancuronium 0.1 mg kg^{-1}. Student's *t* test was used for two-group comparison of neuromuscular blocking effects. Multivariate analysis of variance, including repeated measures, was used to compare the effects on heart rate and arterial pressure. Differences were considered statistically significant if $P \leqslant 0.05$.

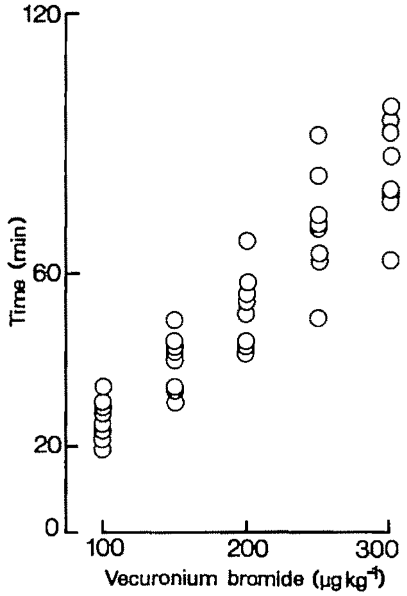


FIG. 2. Effect of increasing dose of vecuronium on the duration of neuromuscular blockade. Experimental conditions as described in the Patients and Methods section.

TABLE II. *Age, weight and body surface area of patients in part II (mean ± SD)*

	n	Age (yr)	Weight (kg)	Body surface (m²)
Vecuronium	10	29.5 ± 10.7	73.3 ± 12.1	1.91 ± 0.2
Pancuronium	10	36.3 ± 9.6	73.5 ± 5.7	1.92 ± 0.1

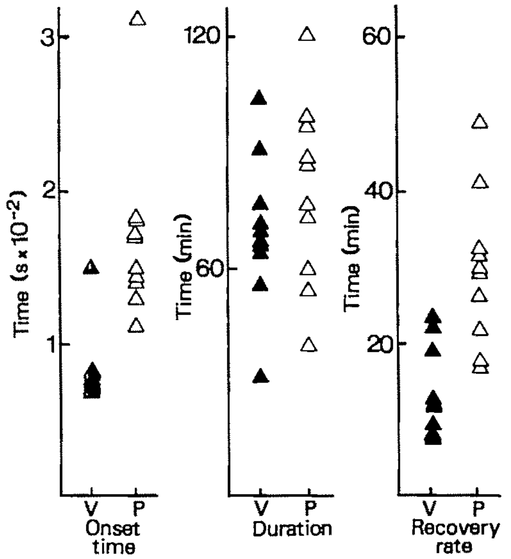


FIG. 3. Comparison of vecuronium (V) 0.3 mg kg^{-1} with pancuronium (P) 0.1 mg kg^{-1} with respect to onset time, duration of neuromuscular block and rate of recovery. Experimental conditions as described in Patients and Methods section.

TABLE III. *Onset time, duration of neuromuscular blockade until 25% recovery and the 25–75% recovery index after vecuronium 0.3 mg kg^{-1} and pancuronium 0.1 mg kg^{-1} (mean ± SEM).* **$P < 0.01$; ***$P < 0.001$

	n	Onset time (s)	Duration (min)	Recovery index (min)
Vecuronium	10	81.0 ± 8.0**	70.1 ± 6.2	13.9 ± 1.9***
Pancuronium	10	168.5 ± 17.3	79.6 ± 7.7	29.3 ± 3.2

RESULTS

Part I

The increases in the dose of vecuronium from 0.1 to 0.3 mg kg^{-1} were associated with decrease in onset time (fig. 1, table I). By increasing the dose of vecuronium (as described in the methods section) significant decreases in onset time were observed with all doses greater than 0.15 mg kg^{-1}. The duration of neuromuscular blockade after the administration of vecuronium increased in a dose-dependent manner (fig. 2, table I). Despite applying different regression models to these data, a non-linear term could not be demonstrated. A linear regression line was subsequently determined by the method of least squares. The dose of vecuronium giving a *mean* duration of action equal to that of pancuronium 0.1 mg kg^{-1} was calculated to be 0.307 mg kg^{-1}. A dose of 0.288 mg kg^{-1} was found to produce a duration of neuromuscular blocking action equal to the *median* duration produced by pancuronium 0.1 mg kg^{-1}. In part II of the study, vecuronium 0.3 mg kg^{-1} was considered as being equivalent to pancuronium 0.1 mg kg^{-1}.

Part II

The groups receiving vecuronium 0.3 mg kg^{-1} ($n = 10$) or pancuronium 0.1 mg kg^{-1} ($n = 10$) were comparable with regard to age, weight and body surface area (table II). As shown in figure 3 and table III, the onset time of vecuronium 0.3 mg kg^{-1} was significantly shorter than that of pancuronium 0.1 mg kg^{-1} ($P < 0.05$). The duration of neuromuscular blockade was the same for both drugs (fig. 3). The recovery index was significantly shorter after vecuronium ($P < 0.001$). A decrease in heart rate ($P < 0.01$), which lasted for 20 min, was seen after the injection of vecuronium ($P < 0.01$) (fig. 4, table IV). When comparing the changes in heart rate following pancuronium or vecuronium there was a significant difference between the two drugs ($P < 0.01$). No significant differences in systolic and mean arterial pressures were seen within or between the vecuronium or pancuronium groups (table IV).

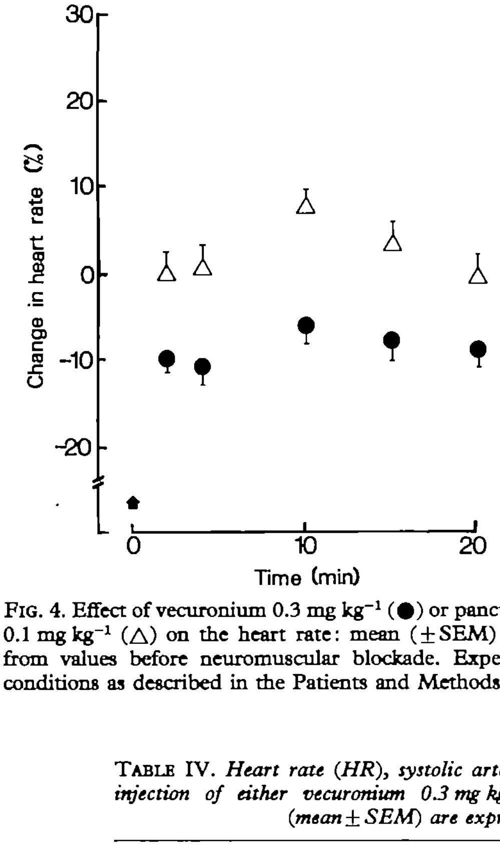


FIG. 4. Effect of vecuronium 0.3 mg kg^{-1} (●) or pancuronium 0.1 mg kg^{-1} (△) on the heart rate: mean (±SEM) changes from values before neuromuscular blockade. Experimental conditions as described in the Patients and Methods section.

DISCUSSION

Vecuronium 0.3 mg kg^{-1} induced neuromuscular blockade which had a duration of action equal to that of pancuronium 0.1 mg kg^{-1}. Using these doses, however, the speed of onset and rate of recovery were about twice as rapid with vecuronium compared with pancuronium. Cardiovascular instability was not seen with either drug.

The relative potency for initial blockade with pancuronium and vecuronium is about 1:1.25 [2]; the dose of vecuronium used in this study (0.3 mg kg^{-1}) was nearly four times as potent as pancuronium 0.1 mg kg^{-1}.

A dose-dependent speed of onset was observed after vecuronium throughout the dose range 0.1–0.3 mg kg^{-1}. Other investigators have reported an apparent ceiling effect when using increasing doses to increase the speed of onset. After the injection of vecuronium 0.1, 0.15 or 0.20 mg kg^{-1}, Mirakhur and co-workers [3] found no difference in onset time between the two larger doses (162 and 177 s, respectively). Similar findings were reported by Casson and Jones [4]. They found decreasing onset times with vecuronium in doses ranging from 0.05 to 0.15 mg kg^{-1}. The differences were negligible with doses of 0.15, 0.2 and 0.4 mg kg^{-1} (99, 95 and 87 s, respectively). A dose-related decrease in onset time after large doses has been observed by Fahey and co-workers [5], who found onset times of 3.8, 2.8 and 2.1 min after 0.07, 0.14 and 0.28 mg kg^{-1}, respectively. Because the speed of onset after vecuronium 0.3 mg kg^{-1} (81 s) is about twice that of pancuronium 0.1 mg kg^{-1} (168 s), the large dose of vecuronium may be useful for rapid tracheal intubation when

TABLE IV. *Heart rate (HR), systolic arterial pressure (SAP) and mean arterial pressure (MAP) after injection of either vecuronium 0.3 mg kg^{-1} (n = 10) or pancuronium 0.1 mg kg^{-1} (n = 10). Results (mean ± SEM) are expressed as percentage of values before injection*

	Time after injection (min)				
	2	4	10	15	20
Vecuronium					
HR	90.4±1.7	89.7±2.1	94.2±2.2	92.4±2.3	91.6±2.1
SAP	98.3±1.1	98.1±1.6	97.5±2.2	97.6±1.6	97.6±1.5
MAP	102.3±3.2	97.0±3.5	103.4±3.9	101.1±3.7	99.4±2.4
Pancuronium					
HR	99.6±2.6	100.3±2.7	107.7±2.2	103.6±2.6	99.8±2.1
SAP	104.2±2.8	103.9±3.5	104.3±2.5	99.6±2.5	102.0±3.1
MAP	104.7±3.3	102.6±3.8	106.3±3.2	104.7±2.5	102.5±3.4

suxamethonium is contraindicated. Rapid onset of neuromuscular blockade with vecuronium may also be achieved using the priming principle, which allows complete blockade after 84 s [6], 75.5 s [7] or 102 s [8]. However, because the priming dose may produce partial muscle weakness [9, 10], a large single dose may be preferable to facilitate rapid tracheal intubation.

The mean duration of action after the large dose of vecuronium was somewhat less than after pancuronium in the second part of the study. However, this difference was not significant ($P = 0.35$). The data on duration of effect in part II are thereby consistent with the results of the initial dose-finding study. The duration of blockade until 25% recovery after pancuronium 0.1 mg kg^{-1} was comparable to the findings of Savarese, Ali and Antonio [11] and Buzello and Nøldge [12]. Using vecuronium 0.2 mg kg^{-1}, Mirakhur and co-workers [3] determined the duration of action to be 55 min. To our knowledge, the effect of larger doses of vecuronium given without inhalation anaesthetics has not been previously studied.

The large dose of vecuronium did not appear to produce a slower rate of recovery. The mean recovery index in our study (13.9 min) was comparable to findings reported after smaller single doses of vecuronium, 11.6 min and 15.5 min after 0.1 and 0.12 mg kg^{-1}, respectively [13].

There was no evidence of cardiovascular instability after pancuronium or the large dose of vecuronium. Absence of cardiovascular side effects from vecuronium has been shown after small doses (0.036 mg kg^{-1}) [14] and after large doses (0.3 mg kg^{-1}) [1]. In our study, heart rate decreased about 10% after vecuronium, which was significantly different from the pancuronium group, in which the values were virtually unchanged. Since atropine was given before induction, all patients had a tachycardia initially and, consequently, the reasons for these changes in heart rate may be complex. The arterial pressure was slightly greater after pancuronium than after vecuronium. This difference, however, was not significant. These observations indicate a greater rate–pressure product after pancuronium 0.1 mg kg^{-1} than after vecuronium 0.3 mg kg^{-1} and may indicate a lower myocardial oxygen consumption in the latter group. Thomson and Putnins [15] demonstrated, in patients undergoing coronary bypass grafting, that myocardial ischaemia was significantly correlated to the value of the rate–pressure product. A large dose of vecuronium may thereby be more beneficial than a standard dose of pancuronium in patients with ischaemic heart disease.

In conclusion, a large dose of vecuronium will have favourable neuromuscular blocking properties by producing a rapid onset of action and a rapid recovery, as well as cardiovascular stability. A large dose of vecuronium may thus provide a safer alternative than a standard dose of pancuronium when long-lasting neuromuscular blockade is desired.

ACKNOWLEDGEMENT

We are grateful to Knut Korsbrekke (Section for Medical Informatics and Statistics, N-5016 Haukeland sykehus University of Bergen, Norway) for statistical evaluation of our data. The excellent technical assistance by Rune Grønnevik R. N. (Department of Anaesthesia, N-5016 Haukeland sykehus) is highly appreciated.

Financial support by Organon Techneca is gratefully acknowledged.

REFERENCES

1. Lienhart A, Desnault H, Guggiari M, Tauvent A, Viars P. Vecuronium bromide: dose-response curve and haemodynamic effects in anaesthetized man. In: Agoston S, ed. *Clinical Experiences with Norcuron*. Amsterdam: Exerpta Medica, 1983; 46–59.
2. Gramstad L, Lilleaasen P. Neuromuscular blocking effects of atracurium, vecuronium and pancuronium during bolus and infusion administration. *British Journal of Anaesthesia* 1985; 57: 1052–1059.
3. Mirakhur RK, Ferres CJ, Clarke RS, Bali IM, Dundee JW. Clinical evaluation of Org NC 45. *British Journal of Anaesthesia* 1983; 55: 119–124.
4. Casson WR Jones RM. Vecuronium induced neuromuscular blockade. The effect of increasing dose on speed on onset. *Anaesthesia* 1986; 41: 354–357.
5. Fahey MR, Morris RB, Miller RD, Sohn YJ, Cronnelly R, Gencarelli P. Clinical pharmacology of Org NC 45 (Norcuron). A new nondepolarizing muscle relaxant. *Anesthesiology* 1981; 55: 6–11.
6. Schwarz S, Ilias W, Lackner F, Mayrhofer O, Foldes FF. Rapid tracheal intubation with vecuronium: the priming principle. *Anesthesiology* 1985; 62: 388–391.
7. Kunjappan VE, Brown EM, Alexander GD. Rapid sequence induction using vecuronium. *Anesthesia and Analgesia* 1986; 65: 503–506.
8. Taboda JA, Rupp SM, Miller RD. Refining the priming principle for vecuronium during rapid-sequence induction of anesthesia. *Anesthesiology* 1986; 64: 243–247.
9. Engbaek J, Howardy-Hansen P, Ording H, Viby-Mogensen J. Precurarization with vecuronium and pancuronium in awake, healthy volunteers: the influence on neuromuscular transmission and pulmonary function. *Acta Anaesthesiologica Scandinavica* 1985; 29: 117–120.

10. Musich J, Walts LF. Pulmonary aspiration after priming dose of vecuronium. *Anesthesiology* 1986; **64**: 517–519.
11. Savarese JJ, Ali HH, Antonio RP. The clinical pharmacology of metocurine; dimethyltubocurarine revisited. *Anesthesiology* 1977; **47**: 277–284.
12. Buzello W, Nøldge G. Repetitive administration of pancuronium and vecuronium (Org NC 45, Norcuron) in patients undergoing long lasting operations. *British Journal of Anaesthesia* 1982; **54**: 1151–1156.
13. Agoston S, Salt P, Newton O, Bencini D, Boomsma P, Erdmann W. The neuromuscular blocking action of Org NC 45, a new pancuronium derivative, in anaesthetized patients. *British Journal of Anaesthesia* 1980; **52**: 53S–59S.
14. Krieg N, Crul JF, Booij LHDJ. Relative potency of Org NC 45, pancuronium, alcuronium and tubocurarine in anaesthetized man. *British Journal of Anaesthesia* 1980; **52**: 783–787.
15. Thomson IR, Putnins CL. Adverse effects of pancuronium during high-dose fentanyl anesthesia for coronary artery bypass grafting. *Anesthesiology* 1985; **62**: 708–713.

Br. J. Anaesth. (1988), **61**, 186–193

CENTRAL AND REGIONAL HAEMODYNAMICS DURING CONTROLLED HYPOTENSION PRODUCED BY ADENOSINE, SODIUM NITROPRUSSIDE AND NITROGLYCERIN

Studies in the Pig

K. NORLÉN

SUMMARY

Controlled hypotension was induced in pigs by the infusion of adenosine, sodium nitroprusside (SNP) or nitroglycerin (TNG). Central and regional haemodynamics were studied using the microsphere technique during control and hypotensive periods. All three drugs produced decreases in mean arterial pressure (MAP), but it was very difficult to maintain stable values of hypotension with TNG, and it was necessary to increase continuously the dose of SNP to produce stable hypotension. Adenosine produced an increase in cardiac output (CO), maintained blood flow to the cerebrum, cerebellum, heart, kidneys and adrenal glands and increased blood flow to the spinal cord and splanchnic organs, except the spleen. SNP and TNG decreased CO, but blood flow to the aforementioned organs (except the spleen) was maintained. Urine flow was greatly impaired during the infusion of adenosine.

Induced hypotension during anaesthesia was introduced by Gardner in 1946 [1]. Reasons for the use of deliberate hypotension during surgery are to facilitate the surgery and to decrease blood loss [2]. However, in a retrospective series [3] there was an overall incidence of complications of more than 3%, and there is always a risk of underperfusion of vital organs—a hazard that the anaesthetist must bear in mind. Many indirect methods have been used to estimate the likelihood of ischaemia in different organs: for example, the electroencephalogram (EEG) [5], the electrocardiogram (ECG) [2] and the measurement of renal function [6]. Direct measurements have been made with flow probes [7], the hydrogen clearance method [8] and the microsphere technique [9]. The latter method has been used for many years in our laboratory [10, 11].

There are many methods for achieving controlled hypotension during clinical anaesthesia; for example, the use of the inhalation agents such as halothane, enflurane and isoflurane [2], direct vasodilators such as nitroglycerin (TNG) [7, 12, 13], sodium nitroprusside (SNP) [4, 6, 7, 13, 14] and purine nucleotides (adenosine and adenosine triphosphate) [13, 15, 16], ganglion and adrenergic receptor blocking agents [2], extradural and spinal block [17] and calcium channel blocking agents [18, 19].

The aim of the present investigation was to study and to compare, using the microsphere technique, the effects on central haemodynamics and regional blood flows of hypotension induced by adenosine nitroprusside and nitroglycerin.

MATERIAL AND METHODS

Anaesthesia and surgical procedures

Nine pigs of both sexes of a Swedish native breed weighing between 19 and 35 kg, were used. They received no food overnight, but had free access to water.

Anaesthesia was induced with ketamine hydrochloride 500 mg (Ketalar, Parke-Davis), and

---

KARIN NORLÉN, M.D., PH.D., Department of Anaesthesiology, University Hospital, S-751 85 Uppsala, Sweden. Accepted for Publication: February 20, 1987.

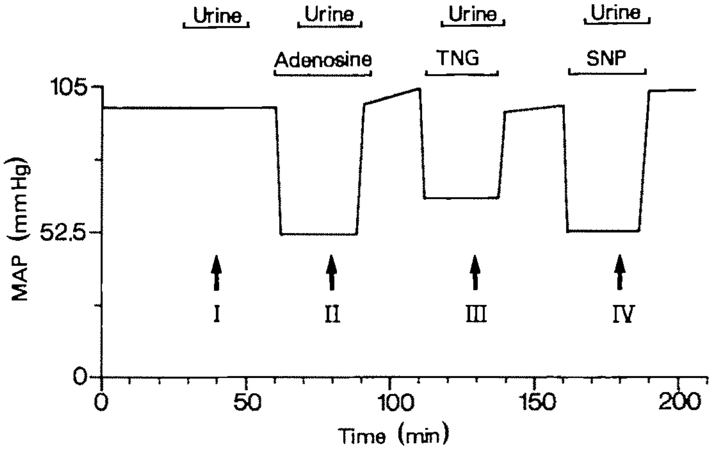


FIG. 1. Design of investigation. The arrows indicate the time of measurements.

atropine 0.5 mg was given i.v. Anaesthesia was maintained with methomidate (Hypnodil, Leo) 7.5 mg h^{-1}/kg body weight. Tracheotomy was performed and the lungs were ventilated by a volume controlled ventilator (Servo 900B, Siemens Elema). Glucose 2.5% in a balanced electrolyte solution (Rehydrex, Pharmacia) 7.5 ml h^{-1} kg^{-1} was administered as a continuous infusion throughout the experiment (this included the fluid in which the hypotensive agent was given). The carotid arteries and the jugular veins were prepared and polyethylene catheters were inserted with their tips lying in the left ventricle, aortic arch and right atrium. A flow-directed catheter with a thermistor was inserted with its tip positioned in the pulmonary artery. One polyethylene catheter was placed in a femoral artery. Catheters were also inserted into the ureters through an incision in the bladder.

Experimental programme (fig. 1)

After catheterization the animals were allowed to stabilize for 40 min. Measurements were made during a period of normotension and during periods of hypotension induced by adenosine, nitroglycerin (TNG) and sodium nitroprusside (SNP). Each period lasted for 30 min, and there was a 20-min recovery period in between the administration of each drug.

SNP and adenosine were given in doses sufficient to decrease MAP from 93.4 ± 11.0 mm Hg to just below 50 mm Hg. When giving TNG it was not possible to obtain a stable level below 60 mm Hg.

Mean arterial (MAP), right atrial (MRAP), pulmonary artery (MPAP) and capillary wedge (MPCWP) pressures, heart rate (HR), CO and urine output were measured at normotension and during the different periods of hypotension. One of the four different labelled microspheres was injected during each period. All the measurements mentioned above were made after 10 min of stable normotension or hypotension. Urine was collected over 20 min. Blood samples for blood-gas analyses were drawn during each period.

At the end of the observation period the animals were killed by injection of potassium chloride into the right atrium and autopsy was performed.

Measurements

MAP, MRAP, MPAP and MPCWP were measured by connecting the above catheters to transducers (EMT-33, Elema Schönander, Sweden). The signals were recorded on a multichannel ink-jet recorder (Mingograph 81, Elema Schönander, Sweden) and the mean pressures were obtained by electronic dampening of the signals. A level of 8 cm below the sternum was used as the zero reference level. Arterial blood samples were analysed for oxygen tension (Po_2), carbon dioxide tension (Pco_2) and pH, using an automatic blood-gas analyser (ABL2, Radiometer AS, Denmark), which also computed base excess (BE).

Cardiac output (CO) was measured using the thermodilution (Cardiac Output Computer, Edwards Labs, Calif., U.S.A.) and the microsphere techniques. Regional blood flows were determined by the microsphere technique. According to Buckberg and colleagues [20] this produces sufficient precision in the blood flow measurements in the organs under investigation. The reference sample was drawn from a small superficial branch of the femoral artery, using a motor syringe at a rate of 1.2 ml min^{-1} (Sage Instrument Syringe, pump 352). The syringe served as a reference organ when calculating blood flows. Immediately before injection into the left ventricle, $2\text{–}3 \times 10^6$ microspheres were suspended in fresh pig plasma to produce a total volume of 1 ml, and agitated in a Vortex JR Mixer. The different microspheres were given sequentially to avoid systematic errors, and so that blood flow could be measured on four different occasions in the same animal.

At postmortem, samples measuring about 1 ml were collected from the heart ($n = 6$ pieces of tissue), lung ($n = 6$), kidney ($n = 4$), adrenal gland ($n = 2$), spleen ($n = 2$), stomach ($n = 2$), intestine ($n = 2$), liver ($n = 2$), pancreas ($n = 2$), muscle ($n = 9$), cerebrum ($n = 3$), cerebellum ($n = 3$) and spinal cord ($n = 8$). These specimens and the reference samples were analysed in a gamma-spectrophotometer (Nuclear, Chicago 1087) with respect to chromium-57, strontium-85, niobium-95 and cerium-141 activity. Correction was made for overlap between the isotopes. The total amount of radioactivity injected was obtained by comparing the activity in the injection syringe before and after the injection of the labelled microspheres.

The blood flow to the different organs (f) (ml $\text{min}^{-1}\,\text{g}^{-1}$) was calculated from the following equation:

$$f = \frac{m \cdot f_s}{m_s} (\text{ml min}^{-1}\,\text{g}^{-1})$$

where m is the radioactivity per gram of specimen, m_s the radioactivity in the reference blood sample and f_s the blood sampling rate in ml min^{-1}. Cardiac output was calculated in the same way, the factor m this time equalling the amount of radioactivity injected.

Calculations and statistics

The systemic vascular resistance (SVR) was calculated from the formula:

$$\text{SVR} = \frac{\text{MAP} - \text{MRAP}}{f} \cdot 10^{-6}\ \text{N s m}^{-5}$$

In the statistical analyses of results the mean, standard deviation (SD) and standard error of the

TABLE I. *General and central haemodynamics during the different periods (mean ± SD).* n = 9. *Significant differences compared with baseline (normotension): *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. CO_t = cardiac output by thermodilution; CO_{st} = cardiac output by microsphere technique; SV = stroke volume; MAP = mean arterial pressure; MRAP = mean right atrial pressure; MPCWP = mean pulmonary capillary wedge pressure; HR = heart rate; SVR = systemic vascular resistance*

	Normotension	Adenosine hypotension	TNG hypotension	SNP hypotension
CO_t (litre min^{-1})	3.6 ± 0.9	4.0 ± 0.7	3.2 ± 0.6*	2.9 ± 0.8
CO_{st} (litre min^{-1})	3.4 ± 0.9	4.1 ± 0.9*	3.1 ± 0.8	2.7 ± 0.7*
SV (ml)	28.1 ± 3.2	36.3 ± 4.6**	21.6 ± 6.0*	18.9 ± 8.4*
MAP (mm Hg)	93.4 ± 11.0	49.4 ± 2.4***	62.3 ± 11.9***	50.3 ± 7.0***
MRAP (mm Hg)	−0.11 ± 0.2	0.33 ± 0.1	−0.33 ± 2.1	−1.9 ± 2.4
MPAP (mm Hg)	18.4 ± 3.9	17.7 ± 3.1	16.7 ± 5.5	12.7 ± 6.0**
MPCWP (mm Hg)	5.9 ± 4.0	5.4 ± 1.7	4.1 ± 1.9	2.3 ± 2.2
HR (beat min^{-1})	123 ± 32.0	113 ± 14.6	143 ± 20.4*	152 ± 36.0*
SVR (10^6 N s m^{-5})	228 ± 60.6	96 ± 21.6***	174 ± 46.2**	168 ± 48.0**
EVF (%)	30.9 ± 3.3	32.7 ± 2.7	32.2 ± 3.2	30.7 ± 4.7
Temp. (°C)	38.3 ± 0.6	38.5 ± 0.5	38.1 ± 0.5	38.4 ± 0.7
Urine (ml min^{-1})	0.39 ± 0.2	0.08 ± 0.1**	0.63 ± 0.5	0.28 ± 0.2
pH	7.46 ± 0.06	7.45 ± 0.04	7.39 ± 0.05	7.41 ± 0.14
Pa_{O_2} (kPa)	12.3 ± 1.9	11.9 ± 2.4	12.6 ± 1.5	11.1 ± 2.0
Pa_{CO_2} (kPa)	5.2 ± 0.4	4.6 ± 0.2	4.6 ± 0.5	4.9 ± 0.3
Base excess (mmol litre^{-1})	2.4 ± 3.9	0.2 ± 2.6	2.7 ± 4.6	−0.9 ± 2.8
Standard bicarbonate (mmol litre^{-1})	26.5 ± 3.6	24.6 ± 2.2	22.2 ± 3.9	23.6 ± 2.4

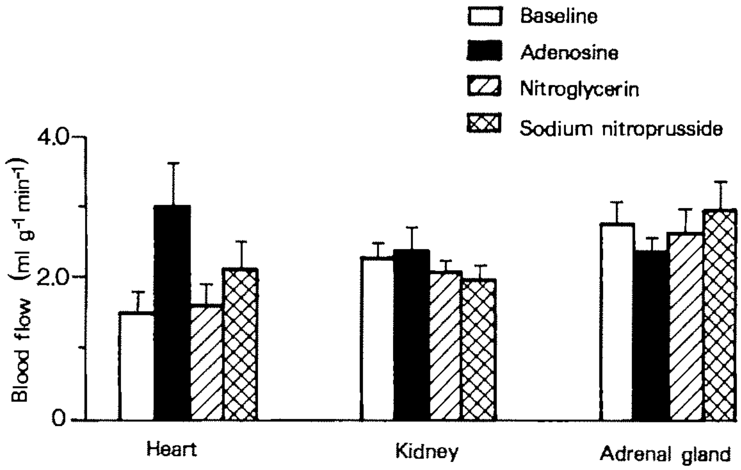


FIG. 2. Blood flow to the heart, kidney and adrenal gland during control conditions and during the different hypotensive periods. Values are mean ± SEM. $n = 9$. Significant differences between control and drug: $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

mean (SEM) were calculated. Changes from baseline to each of the three treatments were tested using paired t test. There was no attempt to compare the individual treatments. A P value of < 0.05 was considered significant.

Linear regression was used in the comparison between the thermodilution and microsphere techniques.

RESULTS

All values are given as mean ± SD. The values obtained during each hypotensive period were compared with the corresponding values obtained during normotension (baseline level).

Hypotension induced by adenosine

Adenosine was given in a dose of 11.5 ± 4.3 μmol kg^{-1} min^{-1}. MAP decreased by 47% from 93.4 + 11.0 mm Hg to 49.4 ± 2.4 mm Hg ($P < 0.001$). MPAP, MPCWP and heart rate were unchanged and no arrhythmias were observed. CO increased by 18%. SVR decreased by 57% ($P < 0.001$). Blood-gas tensions were unchanged (table I). Blood flows to the heart, kidney, adrenal glands (fig. 2), muscles (fig. 3), cerebrum and cerebellum (fig. 4) were unchanged, whereas blood flow to the spinal cord ($P < 0.001$) (fig. 4), the stomach (fig. 5), the small intestine (fig. 5) and the pancreas (fig. 6) ($P < 0.01$) was increased. Blood flow to the spleen decreased ($P < 0.001$) and the blood flow to the liver was unchanged (fig. 6). The urine output decreased from 0.39 ± 0.15 to 0.08 ± 0.06 ml min^{-1} ($P < 0.01$).

Hypotension induced by nitroglycerin

The mean dose of TNG was 119 ± 62 μg kg^{-1} min^{-1} and resulted in a 33% decrease in MAP ($P < 0.001$). There was no change in MRAP, MPAP or MPCWP. HR increased by 16% ($P < 0.05$). CO decreased by 9%. SVR decreased by 24% ($P < 0.01$) (table I).

There were no differences in arterial blood-gas tensions or acid–base balance (table I).

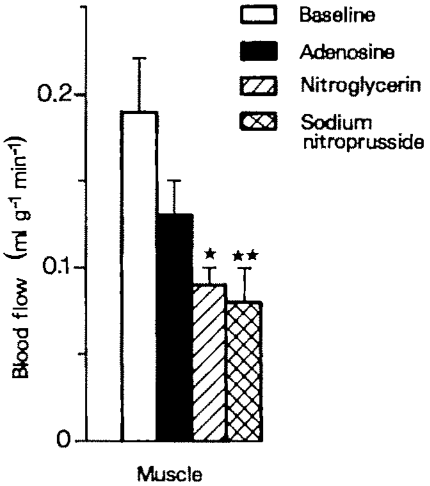


FIG. 3. Blood flow to muscle during control conditions and during the different hypotensive periods. For details see figure 2.

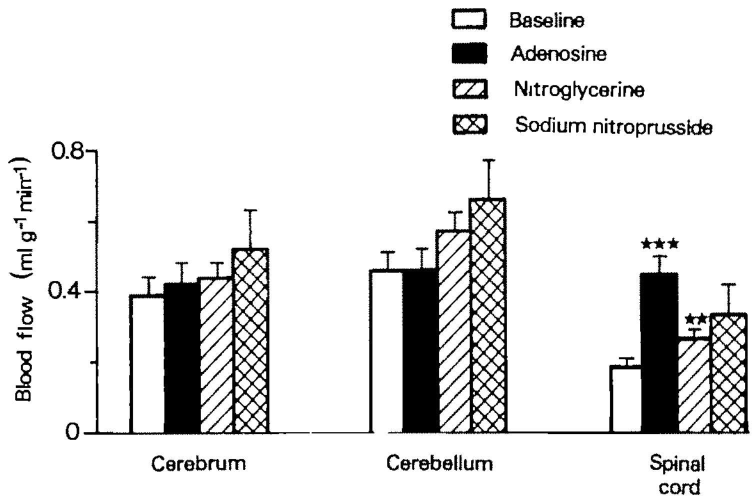


FIG. 4. Blood flow to the cerebrum, cerebellum and spinal cord during control conditions and during the different hypotensive periods. For details see figure 2.

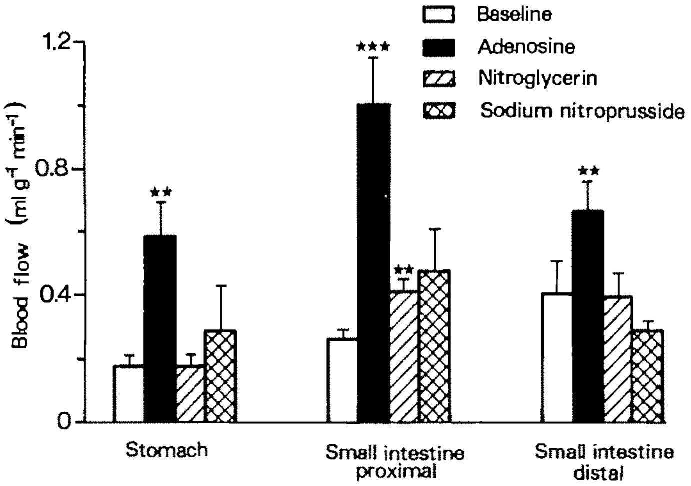


FIG. 5. Blood flow to the liver, pancreas and spleen during control conditions and during the different hypotensive periods. For details see figure 2.

Blood flow to the heart, kidney, adrenal glands (fig. 2), cerebrum, cerebellum, spinal cord (fig. 4), stomach, pancreas and small intestine (figs 5, 6) was maintained. Blood flow to the spleen ($P < 0.05$) (fig. 5) and muscle ($P < 0.05$) (fig. 3) decreased.

The hypotension had no effect on urine output.

Hypotension induced by sodium nitroprusside

SNP was given in a mean dose of 143 ± 165 μg kg^{-1} min^{-1}. It was necessary to increase the dose (from 13 to between 25 and 330 μg kg^{-1} min^{-1}) during the hypotensive period in order to keep the arterial pressure stable.

MAP decreased by 46% ($P < 0.001$). MPAP decreased by 30% ($P < 0.01$). MRAP and MPCWP were unchanged. HR increased by 24% ($P < 0.05$). CO decreased by 21% (table I).

SVR decreased by 27% ($P < 0.01$). There were no changes in arterial blood tensions or acid–base balance (table I). Blood flow to the various organs was unchanged except that blood flow to muscle ($P < 0.01$) (fig. 3) and to the spleen ($P < 0.05$)

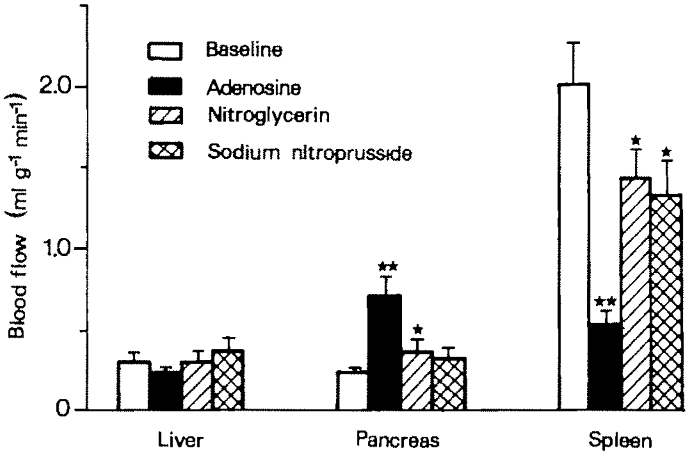


FIG. 6. Blood flow to the stomach and small intestine during control conditions and during the different hypotensive periods. For details see figure 2.

(fig. 5) was decreased. The period of hypotension had no effect on urine output.

DISCUSSION

Previous pilot experiments have shown that CO and central pressures can be maintained stable for 8 h under the conditions of anaesthesia and fluid balance used in these investigations. This study was designed so that all three drugs were given to each animal, with a recovery period between the administrations, so that arterial pressure returned to its baseline value. Adenosine is an endogenous substance and a baseline concentration in the blood is reached within 3–9 min after stopping the infusion [16] so it was therefore given as the first drug. SNP and TNG were then given alternately as the second and third drugs, all in order to minimize the effects of the sequence of drug administration.

Fukunaga, Flacke and Bloor [15] postulated that the actions of adenosine and SNP are of extremely short duration and arterial pressure returns quickly to control. Colley and Sivarajan [21] demonstrated equal regional blood flows before and after hypotension induced by TNG and SNP.

In the present study it was found that it was easy to induce and maintain a stable degree of hypotension with adenosine without any signs of tachyphylaxis. It was necessary to increase the dose of SNP continuously in order to obtain stable hypotension, and this increased tolerance has been reported previously [13, 22, 23]. With TNG it was not possible to obtain a stable value of hypotension below 60 mm Hg, which is similar to findings reported by Colley and Sivarajan [13] and Lagerkranser and colleagues [21]. The difficulties with unstable hypotension when using TNG could be explained in part by the absorption of TNG by the tubing used [24].

Cardiac output (CO) was measured using both the thermodilution and the microsphere techniques, and there was a good correlation between the two methods (correlation coefficient = 0.81). The increased cardiac output and stroke volume seen during adenosine-induced hypotension is explained by the decrease in afterload, as adenosine itself has no inotropic effect [25, 26]. TNG and SNP decrease afterload and preload [27] and there is, therefore, either no change or decreases in CO and stroke volume [28, 29], and these previous findings are in agreement with our results. Reflex tachycardia developed during SNP and TNG infusion [2], but the slowing of the heart rate during adenosine infusion described by Hoffman and co-workers [30] and Lagerkranser and colleagues [26] was not seen. The decrease in heart rate during the infusion of adenosine is presumed to be the result of impaired conduction from atrium to ventricle [31].

One of the risks of induced hypotension is hypoperfusion of vital organs [2]. The brain is the organ of primary concern. Autoregulation in the brain can, however, maintain blood flow in spite of changes in MAP [2, 32]. Autoregulation can be eliminated when using vasodilator drugs, since they influence the vascular bed directly. In this study cerebral and cerebellar blood flow was maintained during all three hypotensive periods, presumably because of preservation of autoregulation and a lack of any direct effect of the hypotensive agents themselves [21, 30, 33]. Newberg, Milde and Michenfelder [34] reported a 50% decrease in cerebral blood flow during adenosine hypotension, but the baseline values of cerebral blood flow were higher in their study. This could possibly be explained by use of different anaesthetic agents.

The blood flow to the spinal cord during very moderate hypotension caused by extradural block has been shown to be maintained or decreased [35] and this is in contrast to what is seen in the present study where there was an increased flow during adenosine- and TNG-induced hypotension. This can be explained by the fact that autoregulation is eliminated and that adenosine and TNG, *per se*, have effects on the spinal vascular bed.

In many other investigations [30, 36, 37] an increase in coronary blood flow has been shown during adenosine hypotension. This increase in flow is said to exceed the oxygen requirements of the myocardium [36]. In the present study the coronary blood flow was not significantly increased.

Blood flow to the kidneys and adrenal glands was maintained during hypotension, but there were great differences in urine flow with the different agents. During adenosine infusion urine flow decreased by 80%, which is supposed to be as a result of a decrease in glomerular filtration rate (GFR) [38, 39]. After adenosine was stopped the urine flow returned to preinfusion values. Tagawa and Vander [38] have also described this and showed also that sodium excretion decreased and increased almost in parallel with the urine flow.

Blood flow to the splanchnic organs other than the spleen was maintained during SNP and TNG hypotensive periods. During adenosine infusion, blood flow to the pancreas, the stomach and the small intestine increased, and this is in accordance with the results of Lagerkranser and colleages [26]. They found that portal venous blood flow increased during adenosine infusion, but that there was a simultaneous decrease in arterial hepatic blood flow. In our experiment arterial hepatic blood flow was not affected. This could be attributable to the use of different experimental animals.

In summary, all three drugs produced hypotension, but it was easiest to produce stable values with adenosine. CO increased during adenosine infusion, whereas it was slightly reduced during TNG and SNP infusions. Blood flow to the vital organs such as the cerebrum, cerebellum, spinal cord, heart, kidney and the splanchnic organs other than the spleen was maintained or increased. Urine flow almost ceased during adenosine hypotension, but returned to control values immediately after the infusion was stopped.

Adenosine, TNG and SNP are all easy to use and the vasodilating effect is instantaneous. The stable hypotension obtained with adenosine, without the necessity of increasing infusion speed, is a great advantage. The major disadvantage with the drug, however, is its effect on urine flow. This must be further studied before adenosine can be used clinically for hypotension of long duration.

ACKNOWLEDGEMENT

This study was supported by grants from the Swedish Medical Research Council, project No. B86-14X-02127-20B, Tore Nilsson Research Fund and the Laerdal Foundation for Acute Medicine. I am grateful for the excellent technical assistance given by Anders Alvfors.

REFERENCES

1. Gardner WJ. The control of bleeding during operation by induced hypotension. *Journal of the American Medical Association* 1946; 132: 572-574.
2. Lam AM. Induced Hypotension. *Canadian Anaesthetists' Society Journal* 1984; 31: 56-62.
3. Little DM. Controlled hypotension. In: *Anesthesia and Surgery*. Springfield, Ill: Thomas, 1956.
4. Tinker JH, Cucchiara RF. *Nitroprusside and Other Short-Acting Hypotensive Agents*. 1st edn. Boston: Little, Brown and Co., 1978; 89-112.
5. Astrup J, Symon L, Branston NM, Lassen NA. Cortical evoked potential and extracellular K^+ and H^+ at critical levels of brain ischemia. *Stroke* 1977; 8: 51-57.
6. Behnia R, Siqueira EB, Brunner EA. Sodium nitroprusside-induced hypotension: Effect on renal function. *Anesthesia and Analgesia* 1978; 57: 521-526.
7. Panzenbeck MJ, Arsenio B, Kaley G. Nitroglycerin and nitroprusside increase coronary blood flow in dogs by a mechanism independent of prostaglandin release. *American Journal of Cardiology* 1984; 53: 936-940.
8. Essen van C, Kistler IP, Lees RS, Zervas NT. Cerebral blood flow and intracranial pressure in the dog during intravenous infusion of nitroglycerin alone and in combination with dopamine. *Stroke* 1981; 12: 331-338.
9. Wagner HN jr, Rhodes BA, Sasaki Y, Ryan JP. Studies of the circulation with radioactive microspheres. *Investigative Radiology* 1963; 4: 374-386.
10. Norlén K, Rentzhog L, Wikström S. Microsphere

measurement of regional intestinal blood supply and cardiac output in the rat. *Upsala Journal of Medical Science* 1978; **83**: 163–166.

11. Haldén E, Jakobson S, Janerås L, Norlén K. Effects of positive end-expiratory pressure on cardiac output distribution in the pig. *Acta Anaesthesiologica Scandinavica* 1982; **26**: 403–408.
12. Fahmy, NR. Nitroglycerin as a hypotensive drug during general anesthesia. *Anesthesiology* 1978; **49**: 17–20.
13. Lagerkranser M, Sollevi A, Irestedt L, Tidgren B, Andrén M. Renin released during controlled hypotension with sodium nitroprusside, nitroglycerin and adenosine: a comparative study in the dog. *Acta Anaesthesiologica Scandinavica* 1985; **29**: 45–49.
14. Moraca PP, Bitte EM, Hale EE, Vasnuth CE, Poutasse EF. Clinical evaluation of sodium nitroprusside as a hypotensive agent. *Anesthesiology* 1962; **23**: 193–199.
15. Fukunaga AF, Flacke WE, Bloor BC. Hypotensive effects of adenosine and adenosine triphosphate compared with sodium nitroprusside. *Anesthesia and Analgesia*, 1982; **61**: 273–278.
16. Sollevi A, Lagerkranser M, Irestedt L, Gordon E, Lindquist C. Controlled hypotension with adenosine in cerebral aneurysm surgery. *Anesthesiology* 1984; **61**: 400–405.
17. Bromage PR. *Epidural Analgesia*. 1st edn. Philadelphia: W.B. Saunders Company, 1978; 500–501.
18. Zimpfer M, Fitzal S, Tonczer L. Verapamil as a hypotensive agent during neuroleptanaesthesia. *British Journal of Anaesthesia* 1981; **53**: 885–889.
19. Cottrell JE, Giffin JP, Hartung J, Shwiry B. Intracranial pressure during nifedipine-induced hypotension in cats. *Anesthesia and Analgesia* 1983; **62**: 254.
20. Buckberg GD, Luck JC, Payne B, Hoffman JIE, Archie JP, Fixler DE. Some sources of error in measuring regional blood flow with radioactive microspheres. *Journal of Applied Physiology* 1971; **31**: 598–604.
21. Colley PS, Sivarajan M. Regional blood flow in dogs during halothane anesthesia and controlled hypotension produced by nitroprusside and nitroglycerin. *Anesthesia and Analgesia* 1984; **63**: 503–510.
22. Rudehill A, Gordon E, Lagerkranser M. Sodium nitroprusside as a hypotensive agent in intracranial aneurysm surgery. *Acta Anaesthesiologica Scandinavica* 1979; **23**: 404–410.
23. Krey VAW, In: Scriabine A, ed. *Pharmacology of Antihypertensive Drugs*. New York: Raven Press, 1980; 373–396.
24. Wagner W. Current concepts of i.v. nitroglycerin therapy. *National Intravenous Therapy Association* 1983; **6**: 342–344.
25. Gross, GJ, Waltier DC, Hardman HF. Effect of adenosine on myocardial oxygen balance. *Journal of Pharmacology and Experimental Therapeutics* 1976; **196**, 445–454.
26. Lagerkranser DM, Irestedt L, Sollevi A, Andreen M. Central and splanchnic hemodymanics in the dog during controlled hypotension with adenosine. *Anesthesiology* 1984; **60**: 547–552.
27. Gerson JI, Forrest BA, Seltzer JL, Parker FB, Markowitz AH. Arterial and venous dilation by nitroprusside and nitroglycerin—is there a difference? *Anesthesia and Analgesia* **61**: 1982; 256–260.
28. Lagerkranser M, Gordin E, Rudehill A. Cardiovascular effects of sodium nitroprusside in cerebral aneurysm. *Acta Anaesthesiologica Scandinavica* 1980; **24**: 426–432.
29. Lagerkranser M. Cardiovascular effects of nitroglycerin as a hypotensive agent in cerebral aneurysm surgery. *Acta Anaesthesiologica Scandinavica* 1982; **26**: 453–457.
30. Hoffman WE, Satinover I, Miletich DJ, Albrecht RF, Gans BJ. Cardiovascular changes during sodium nitroprusside or adenosine triphosphate infusion in the rat. *Anesthesia and Analgesia* 1982; 61: 99–103.
31. Drury AN, Szent-Györgyi A. The physiological activity of adenine compounds with especial reference to their action upon the mammalian heart. *Journal of Physiology (London)* 1929; **68**: 213–237.
32. Lassen NA, Christensen MS. Physiology of cerebral blood flow. *British Journal of Anaesthesia* 1976; **48**: 719–734.
33. Maruno Y, Hashimoto Y, Saito N, Okazaki N, Fujii A, Aono M. The effects of 50% hypotension induced by ATP, sodium nitroprusside and trimethaphan on canine cerebral blood flow and metabolism. *Japanese Journal of Anesthesiology* 1978; **27**: 1525–1532.
34. Newberg LA, Milde JH, Michenfelder JD. Cerebral and systemic effects of hypotension induced by adenosine or ATP in dogs. *Anesthesiology* 1985; **62**: 429–436.
35. Feuk U, Alvfors A, Jakobson S, Norlén K. Cirkulationsanpassning vid övertrycksandning och samtidig thoracal epiduralanestesi. *Opuscula Medica* 1985; **30**: 9.
36. Wolf MM, Berne RM. Coronary vasodilator properties of purine and pyrimidine derivatives. *Circulation Research* 1956; **4**: 343–348.
37. Rowe GG, Alfonso S, Gurtner DH, Chelius C, Lowe W, Castillo C, Crumpton C. The systemic and coronary hemodynamic effects of adenosine triphosphate and adenosine. *American Heart Journal* 1962; **64**: 228–234.
38. Tagawa H, Vander AI. Effects of adenosine compounds on renal function and renin secretion in dogs. *Circulation Research* 1970; **26**: 327–338.
39. Spielman WS, Thompson CI. A proposed role for adenosine in the regulation of renal hemodynamics. *American Journal of Physiology* 1982; **242**: F423–F435.

Br. J. Anaesth. (1988), **61**, 194–199

HAEMODYNAMIC AND HEART RATE REFLEX RESPONSES TO PROPOFOL IN THE RABBIT

Comparison with Althesin

D. W. BLAKE, B. JOVER AND B. P. McGRATH

SUMMARY

Propofol was administered to eight rabbits by constant i.v. infusion at 0.2, 0.4 and 0.6 mg kg^{-1} min^{-1} to produce light sedation. The lowest dose was compared with an infusion of Althesin 0.1 mg kg^{-1} min^{-1}. The rabbits had been previously implanted with aortic and vena caval perivascular balloon cuffs to examine the baroreceptor–heart rate reflex and an aortic thermistor catheter for cardiac output (CO) measurements. A silastic catheter was placed in the pericardial sac so that the cardiac nerves could be blocked with local anaesthetic. Mean arterial pressure (MAP) was well maintained with all anaesthetic infusions. At the lower doses of propofol, CO increased by 20% ($P < 0.01$) with a corresponding decrease in total peripheral resistance (TPR). However, CO and TPR were not changed significantly by Althesin. Both anaesthetics induced a similar tachycardia. Cardiac nerve blockade did not abolish the different CO and TPR responses observed for the two agents. A dose-related reduction in the range and gain of the baroreceptor–heart rate reflex was observed with propofol ($P < 0.05$). The pattern of alteration of the reflex curve, however, differed between the two anaesthetics and the vagal efferent component was more resistant to blockade with propofol. The relative preservation of baroreceptor reflex responses, and the reduction in TPR by a reduction of resting constrictor tone, suggest propofol may have significant clinical advantages when used as a sedative infusion.

Propofol (Diprivan, ICI) provides satisfactory anaesthesia and its pharmacokinetic profile makes it suitable for use by continuous infusion [1, 2]. However, the pattern of haemodynamic changes in response to the administration of propofol is complex. In clinical studies propofol has been reported to produce decreases in arterial pressure, cardiac output (CO) and total peripheral vascular resistance (TPR) of varying degree, whereas heart rate was maintained [3–6]. In some circumstances more marked arterial hypotension has occurred and this may limit the use of propofol for major surgery [7]. The presence of other anaesthetics and the nature of ventilatory control influence such responses.

In the absence of other anaesthetics, single doses or infusions of propofol have been reported to decrease MAP and cardiac output by less than 20% [5,6], whereas greater decreases occurred with propofol plus nitrous oxide [7,8]. The decrease in systemic vascular resistance with propofol appears to be significantly greater than that following the administration of Althesin or thiopentone [4,8]. Although the mechanism of the decrease in resistance is unknown, studies in the isolated cat hind-limb suggest that 2–6 diisopropol phenol formulated in Cremophor had some direct vasodilator activity [9]. An alternative explanation is that propofol may alter baroreceptor function, resulting in reduced sympathetic vascular tone. However, at least some baroreceptor-mediated responses may be well preserved during propofol anaesthesia in man [10].

It is unclear from clinical data whether the hypotensive effects of propofol are principally from direct depression of the myocardium and

---

D. W. BLAKE, M.B., B.S., B. MED. SC., PH.D., F.F.A.R.A.C.S. (Department of Anaesthesia); B. JOVER, M.SC., B. P. McGRATH, M.B., B.S., M.D., F.R.A.C.P. (Monash University Department of Medicine); Prince Henry's Hospital, St Kilda Rd, Melbourne, Australia, 3004. Accepted for Publication: December 23, 1986.

vascular smooth muscle, or from effects on autonomic reflex pathways. Direct depressant actions are likely to be dose-related, but reflex effects might occur at lower sedative doses and reduce the cardiovascular margin of safety.

Since propofol closely resembles Althesin in its pharmacokinetics and likely clinical applications, the two agents were compared in the present study in the rabbit. The experiments were designed to study haemodynamic and reflex responses to propofol using techniques that would not be tolerated in human subjects. Chronically implanted balloon cuffs were used to manipulate arterial pressure and determine baroreceptor–heart rate reflex function. Furthermore, in the same animals, it was possible to assess the effect on haemodynamics of temporarily denervating the heart. This was achieved by injecting local anaesthetic via a chronic pericardial catheter [11]. These techniques enabled an analysis of the role of the cardiac nerves and baroreceptor reflexes in maintaining cardiac output and total peripheral resistance during anaesthesia.

MATERIALS AND METHODS

Investigations were in eight cross-bred rabbits of either sex, weighing 2.4–3.1 kg. Preliminary operations were performed after induction of anaesthesia with thiopentone, tracheal intubation and ventilation with an air–halothane mixture.

At the first operation a thermistor catheter was placed in the infra-renal aorta via the iliolumbar artery [12]. A right-sided thoracotomy was also performed and an inflatable cuff placed around the inferior vena cava. At a second operation 2 weeks later, a left thoracotomy was performed and a cuff placed on the descending thoracic aorta. A small silastic catheter was also inserted into the pericardial sac and sutured in place. A disc of nylon was used to seal the opening in the pericardium. A further 2 weeks recovery was allowed before the start of the definitive investigation.

Catheters were inserted in a central ear artery and vein before each study under local anaesthesia (0.5 % lignocaine). A central venous catheter was also introduced via an external jugular vein. Tubing connecting to the perivascular balloons and the thermistor wires was buried subcutaneously between experiments.

Each rabbit was studied on three separate days using different anaesthetic infusions:

(1) low-dose propofol: 1.5-mg kg^{-1} bolus + 0.2 mg kg^{-1} min^{-1} i.v.;
(2) cumulative dose propofol 1.5 mg kg^{-1} + 0.2, 0.4 and 0.6 mg kg^{-1} min^{-1};
(3) Althesin 1 mg kg^{-1} + 0.1 mg kg^{-1} min^{-1}.

A random order was used and at least 2 days allowed for recovery between experiments. The dose of Althesin used was known from previous rabbit studies to produce light anaesthesia with loss of eyelash and righting reflexes, but without significant ventilatory depression or loss of the corneal reflex. This had been found to be suitable for the assessment of autonomic reflexes without significant direct cardiovascular depression [13]. The doses of propofol were chosen according to the reported relative potencies of propofol and Althesin in man [4,14]. Arterial blood-gas tensions were measured randomly, but were not altered significantly by any of the anaesthetic infusions.

Arterial pressure and right atrial pressure (RAP) were measured with Hewlett–Packard transducers and recorded on a "Gould" chart recorder. Heart period (HP, pulse interval) was also measured directly from the arterial pulse with a pulse interval meter. All measurements of cardiac output were averaged from six thermodilution curves and total peripheral resistance was calculated using mean arterial pressure (MAP) and right atrial pressure. Measurements were made in the awake animal and after the anaesthetic had been infused for 40, 60 and 80 min.

Baroreceptor reflex curves, relating MAP to pulse interval, were derived from graded inflations of the aortic and IVC balloon cuffs to increase and decrease MAP, respectively [15]. In individual animals, reflex measurements were based on a total of 12 balloon inflations over a period of 15–20 min. Each inflation was maintained for about 40 s and the heart rate response in the final 10 s recorded. Sigmoid curves were fitted to these data using a logistic transformation and described by four variables (table II, fig. 2): lower plateau, heart period range, average gain and arterial pressure at middle of heart period range (AP_{50}). These variables were averaged to obtain pooled data from the group of animals.

Temporary blockade of efferent and afferent cardiac nerves was achieved by injection of 1 ml of 2 % procaine via the pericardial catheter. This was repeated after 10–15 min. The efficacy of the block was confirmed if the heart rate responses to balloon inflations were abolished [11]. Injections of 1 ml of physiological saline intrapericardially or of 2% procaine 1 ml systemically produced no detectable response.

After insertion of the catheters, the rabbits rested in an experiment box for 20 min before measurement of control circulatory variables and baroreceptor–heart rate reflex curves. The relevant anaesthetic was then infused for 60 min, the baroreflex curve being repeated between 45 and 60 min. After 60 min of anaesthesia with either low-dose propofol or Althesin, the cardiac nerves were blocked with procaine and the infusion of the of the anaesthetic continued for 20 min. In the experiments in which cumulative doses of propofol were studied, the rate of infusion was doubled at 40-min intervals.

Two-way analysis of variance was performed on the haemodynamic data and the indices of baroreceptor reflex activity. Orthogonal partitioning of the treatments sum of squares was used to compare the effects of the anaesthetic infusions and cardiac blockade within animals [16]. The results are expressed with either the standard error of the mean, or standard error of the difference, obtained from the analysis of variance.

RESULTS

The infusions of Althesin and the two lower doses of propofol produced similar levels of light anaesthesia. There was loss of the eyelash and righting reflexes, but a persisting response to noxious stimuli and a corneal reflex. The highest propofol dose induced deeper anaesthesia with a lack of response to noxious stimuli, but no significant alteration in blood-gas tensions.

Circulatory responses to anaesthesia

Control values for MAP, RAP, CO, TPR and heart rate did not vary significantly in the same animal on the three experiment days, indicating that resting conditions were achieved and that there were no lasting circulatory effects from any treatment.

Propofol did not alter MAP at the two lower infusion rates, but at 0.6 mg kg^{-1} min^{-1} there was a small reduction of 7±4 mm Hg (table I). However, CO was increased significantly ($P < 0.05$) by 30±6% and 23±6% with propofol infusions of 0.2 and 0.4 mg kg^{-1} min^{-1}, respectively. This was associated with a corresponding decrease in TPR. When the infusion of propofol was increased to 0.6 mg kg^{-1} min^{-1}, CO decreased, although TPR remained less than the control values obtained in the awake animal. Heart rate increased progressively with increasing doses of propofol, to be 24±6% above control at the highest infusion rate ($P < 0.01$).

The responses to propofol 0.2 mg kg^{-1} min^{-1} and Althesin 0.1 mg kg^{-1} min^{-1} are compared in figure 1. Neither significantly altered MAP and there were similar increases in heart rate (18±6% and 20±6%). The changes in CO and TPR were different during propofol compared with Althesin infusion ($P < 0.01$) (fig. 1). Propofol increased CO after 40 and 60 min by 19% and 15%, respectively, associated with a reduction in TPR. However, CO and TPR were not significantly changed during the infusion of Althesin.

Blockade of the cardiac nerves

Intra-pericardial procaine during infusions of propofol or Althesin reduced heart rate to values similar to (pre-anaesthesia) control ($P < 0.01$) (fig. 1); MAP was not altered significantly. CO was reduced in both groups ($P < 0.01$), but the difference in TPR was maintained, remaining below control in the propofol-treated animals with cardiac block, but being significantly in-

TABLE I. *Average circulatory variables* (n = 6) *for the awake animal (control) and after 40-min periods of propofol infusion. Standard error of the mean (SEM) represents the within animal variance for the effects of anaesthesia derived from two-way analysis of variance as (error mean square*/n)

	Control	Propofol infusion (mg kg^{-1} min^{-1}) 0.2	0.4	0.6	SEM
MAP (mm Hg)	87	87	89	80	2.9
RAP (mm Hg)	0.9	0.8	−0.1	0.3	0.8
CO (ml min^{-1})	834	1036	1010	847	52
TPR (units)	104	84	88	91	5.5
HR (beat min^{-1})	220	256	269	273	13.6

creased in the Althesin group with cardiac block ($P < 0.05$).

Baroreceptor–heart rate reflex

Sigmoid curves relating MAP to heart period (HP, pulse interval) were fitted to the data from individual experiments. The averaged variables (table II) were then used to construct the curves in figure 2. The indices of the control baroreflex curves, obtained in the awake animals, showed no significant differences between each of the three experiment days. The (control) curve indices in table II are, therefore, averaged from the three experiments.

The infusions of propofol produced a dose-related reduction in the heart period range of the MAP–HP curve from 256 to 108 ms ($P < 0.01$) (fig. 2). This was a result of alterations in the

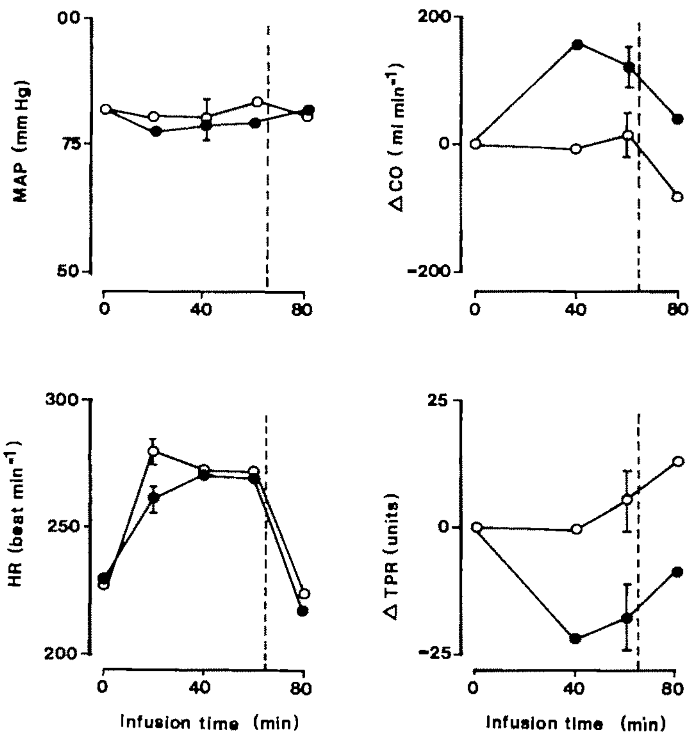


FIG. 1. Circulatory responses to 80-min infusions of propofol and Althesin. The cardiac nerves were blocked with 2% procaine after 60 min. MAP = Mean arterial pressure; ΔCO = change in cardiac output from control; ΔTPR = change in total peripheral resistance; HR = heart rate. Error bars indicate SEM from analysis of variance. Vertical dashed line indicates cardiac block.

TABLE II. *Average baroreceptor–heart rate reflex variables* (n = 6). *Standard error of mean (SEM) based on within-animals variance from analysis of variance.* AP_{50} *= Arterial pressure at mid heart period range (HP range)*

	HP range (ms)	Av. gain (ms (mm Hg)$^{-1}$)	AP_{50} (mm Hg)	Lower plateau (ms)
Av. control	256	14.5	82.3	185
Propofol				
0.2 ml kg^{-1} min^{-1}	205	10.7	82.5	175
0.4 ml kg^{-1} min^{-1}	141	6.8	81	180
0.6 ml kg^{-1} min^{-1}	108	3.3	80.2	188
Althesin	120	1.7	93	182
SEM	28.1	1.1	2.4	8.6

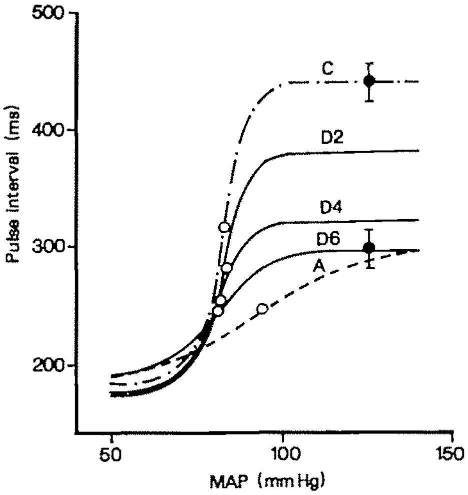


FIG. 2. Averaged ($n = 6$) baroreceptor reflex curves. Control curve (C) obtained in awake animal. D2, D4 and D6 = Propofol 0.2, 0.4 and 0.6 mg kg^{-1} min^{-1}, respectively. A = Althesin 0.1 mg kg^{-1} min^{-1}. Error bars indicate SEM for heart period range. ○ = AP_{50} (mean arterial pressure (MAP) at mid heart period range).

upper plateau of the curve; that is, the vagal efferent component of the reflex. Reflex gain was reduced at the higher doses of propofol infusion by 7.7 and 11.2 ± 1.6 ms (mm Hg^{-1}) ($P < 0.05$).

The infusion of Althesin reduced the gain and range of the reflex ($P < 0.05$) to values similar to those after infusion of propofol 0.6 mg kg^{-1} min^{-1}. There was also a small increase of 11 ± 3 mm Hg in the median arterial pressure ($P < 0.05$). None of the anaesthetic infusions significantly influenced the lower plateau of the curve; that is, the maximum tachycardia.

DISCUSSION

The haemodynamic responses to propofol in the rabbit have important similarities with those described in clinical studies. In the present study, total peripheral resistance was reduced at each dose of propofol and this was the principal difference between the effects of propofol and Althesin. A reduction in cardiac output has generally been reported in man. However, the doses of propofol used in these clinical studies were selected so as to provide deeper levels of anaesthesia, and such doses are likely to depress myocardial function directly. In contrast in the present study, the haemodynamic effects of propofol were examined in animals in the absence of any influences of surgical procedures or other drugs likely to cause myocardial depression. MAP and CO were reduced in the rabbit as the dose of propofol was increased, suggesting that a dose-related direct depression of cardiovascular function also occurs in this species. The increase in heart rate after propofol appears to contrast with the reported responses in man. However, the changes in the baroreceptor–heart rate reflex after propofol indicate that the maximum bradycardia and location of the curve are only slightly changed. Therefore, the higher resting heart rate after propofol in the rabbit, compared with results in clinical studies, may only reflect a different balance of vagal and sympathetic tone in the absence of surgery.

Tachycardia during the infusion of Althesin is caused by both reduction of vagal tone and increased sympathetic activity [13]. Cardiac denervation reduced resting heart rate by similar amounts during the two anaesthetic infusions, suggesting that there had been a comparable increase in cardiac sympathetic activity in each case before blockade with procaine. The smaller increase in heart rate after 40 min of propofol compared with Althesin probably reflects a lesser degree of vagal block with propofol, as found in the baroreceptor–heart rate reflex responses.

Propofol was also much less potent than Althesin in causing depression of baroreceptor–heart rate reflex responses. In previous studies in the rabbit we reported that Althesin caused less reflex depression than equivalent doses of thiopentone or ketamine. The latter appeared to act more proximally on the baroreflex arc and to alter both vagal and sympathetic responses [17]. It is likely that propofol and Althesin also act on reflex pathways at different central nervous system sites, as there were qualitative differences in their effects on the baroreflex curves. No shift in the location of the curve was seen with propofol and the reflex range was reduced independently from the gain at the lower propofol doses. However, neither propofol nor Althesin altered the sympathetic efferent component of the heart rate responses, in contrast to comparable doses of other anaesthetics.

Cardiac efferent and afferent nerves can be blocked rapidly and reversibly by the intrapericardial injection of local anaesthetic, without significant systemic effects [11]. Complicating central nervous system or peripheral vascular effects that might follow the systemic infusion of receptor blocking drugs are also avoided. Loss of the cardiac sympathetic responses after intrapericardial procaine reduced CO by similar amounts during propofol and Althesin anaesthesia and in each case, MAP was maintained by an increase in TPR. Therefore, reflex peripheral vasoconstrictor responses could still be induced following low doses of either of these anaesthetics. This is in keeping with the lesser degree of depression of the heart rate reflexes with these agents compared with thiopentone or ketamine.

Increases in TPR during low-dose anaesthetic infusions can result from depression of the afferent limb of arterial baroreceptor reflexes and disinhibition of vasoconstrictor tone [13]. Input from low pressure cardiac receptors, however, is also thought to modulate arterial baroreceptor responses [18] and effects on this input might account for the differences in vasoconstrictor tone during propofol compared with Althesin anaesthesia. A significant direct vasodilator action of propofol in the doses used is unlikely, so the observed decrease in TPR with propofol in these experiments probably reflects reflex changes in sympathetic tone. It is likely that the input of cardiac afferents was involved in this reflex as, after blockade of both cardiac efferents and afferents, cardiac output and total peripheral resistance returned almost to pre-anaesthetic resting values.

These investigations suggest that the infusion of propofol in sedative doses results in a beneficial reduction in cardiac afterload with preservation of autonomic reflex function. However, when dosage is increased and reflexes are blocked by the administration of other drugs, direct depressant actions may be unmasked. This animal study suggests that the ideal clinical use of propofol may be as a supplement to regional anaesthesia rather than as a component of general anaesthesia for major surgery.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the expert technical assistance of Miss E. Trigg and Mr S. Wood. The experiments were supported by a grant from the Senior Medical Staff Fund, Prince Henry's Hospital, Melbourne. Propofol was supplied by I.C.I.

REFERENCES

1. Mackenzie N, Grant IS. Comparison of propofol with methohexitone in the provision of anaesthesia for surgery under regional blockade. *British Journal of Anaesthesia* 1985; 57: 1167–1172.
2. Cockshott IC. Propofol ('Diprivan') pharmacokinetics and metabolism—an overview. *Postgraduate Medical Journal* 1985; **61** (Suppl. 3): 45–50.
3. Aun C, Major E. The cardiorespiratory effects of ICI 35868 in patients with valvular heart disease. *Anaesthesia* 1984; **39**: 1096–1100.
4. Prys-Roberts C, Davies JR, Calverley RK, Goodman NW. Haemodynamic effects of infusions of diisopropyl phenol (ICI 35868) during nitrous oxide anaesthesia in man. *British Journal of Anaesthesia* 1983; **55**: 105–111.
5. Grounds RM, Twigley AJ, Carli F, Whitwam JG, Morgan M. The haemodynamic effects of intravenous induction: comparison of the effects of thiopentone and propofol. *Anaesthesia* 1985; **40**: 735–740.
6. Stephan H, Sonntag H, Schenk HD, Kettler D, Khambatta, HJ. Effects of propofol on cardiovascular dynamics, myocardial blood flow and myocardial metabolism in patients with coronary artery disease. *British Journal of Anaesthesia* 1986; **58**: 969–975.
7. Coates DP, Prys-Roberts C, Spelina KR, Monk CR, Morley I. Propofol (Diprivan) by intravenous infusion with nitrous oxide: dose requirements and haemodynamic effects. *Postgraduate Medical Journal* 1985; **61** (Suppl. 3): 76–79.
8. Patrick MR, Blair IJ, Feneck RO, Sebel PS. A comparison of the haemodynamic effects of propofol ('Diprivan') and thiopentone in patients with coronary artery disease. *Postgraduate Medical Journal* 1985; **61** (Suppl. 3): 23–27.
9. Glen JB. Animal studies of the anaesthetic activity of ICI 35868. *British Journal of Anaesthesia* 1980; **52**: 731–741.
10. Prys-Roberts C. Haemodynamic effects of "Diprivan" infusion anaesthesia: comparison with other intravenous and volatile anaesthetics. In: Proceedings of the VII European Congress of Anaesthesiology, Abstracts III, 1986; 296.
11. Dorward PK, Flaim M, Ludbrook J. Blockade of cardiac nerves by intra-pericardial local anaesthetics in the conscious rabbit. *Australian Journal of Experimental Biology and Medical Science* 1983; **61**: 219–230.
12. Korner PI, Hilder RG. Measurement of cardiac output and regional blood flow by thermodilution. *Clinical and Experimental Pharmacology and Physiology* 1974; **1** (Suppl. 1), 47–66.
13. Blake DW, Korner PI. Role of baroreceptor reflexes in the haemodynamic and heart rate responses to Althesin, ketamine and thiopentone anaesthesia. *Journal of the Autonomic Nervous System* 1981; **3**: 55–70.
14. Sear JW, Prys-Roberts C. Dose related haemodynamic effects of continuous infusions of Althesin in man. *British Journal of Anaesthesia* 1979; **51**: 867–873.
15. Korner PI, Shaw J, West MJ, Oliver JR. Central nervous system control of baroreceptor reflexes in the rabbit. *Circulation Research* 1972; **31**: 637–652.
16. Snedecor GWA, Cochran WG. *Statistical Methods*. 6th edn. Iowa State University Press, 1967; 301.
17. Blake DW, Blombery PA, Korner PI. Effect of ketamine, Althesin and thiopentone on the valsalva-constrictor and heart rate reflexes of the rabbit. *Journal of the Autonomic Nervous System* 1982; **5**: 291–301.
18. Ludbrook J, Graham WF. The role of cardiac receptor and arterial baroreceptor reflexes in control of the circulation during acute change of blood volume in the conscious rabbit. *Circulation Research* 1984; **54**: 424–435.

Br. J. Anaesth. (1988), **61**, 200–205

EFFECTS OF INHALATION ANAESTHETICS ON FILTRATION OF VENOUS GAS EMBOLI BY THE PULMONARY VASCULATURE

J. KATZ, B. C. LEIMAN AND B. D. BUTLER

SUMMARY

Venous gas emboli are prevented from reaching the systemic circulation by filtration in the pulmonary vasculature. This filtration can be overwhelmed by exceeding certain critical rates of venous air infusion. To characterize further these filtration phenomena, the effects of pentobarbitone, isoflurane and halothane anaesthesia on the incidence of spillover of venous bubbles into the arteries were studied in groups of nine dogs. Venous air was infused at rates of 0.25, 0.30, and 0.35 ml kg^{-1} min^{-1}. Spillover of venous bubbles into the arteries was detected with a Doppler ultrasonic probe located over the suprarenal aorta. At the lowest venous air dose (0.25 ml kg^{-1} min^{-1}), no bubbles were detected in the systemic circulation in the pentobarbitone- or halothane-anaesthetized dogs, while arterial bubbles were detected in two with isoflurane anaesthesia. At 0.30 ml kg^{-1} min^{-1} air, one, four and two dogs had arterial bubbles detected with pentobarbitone, halothane or isoflurane anaesthesia, respectively, while at 0.35 ml kg^{-1} min^{-1} spillover of bubbles occurred in four, five and three, respectively. The spillover of venous bubbles into the arteries was dose-related for the pentobarbitone- and halothane-anaesthetized dogs.

The effects of arterial air embolism can be catastrophic as intravascular bubbles can obstruct the blood supply to vitally important organs. Sources of air on the arterial side of the circulation include those of venous origin which cross into the systemic circulation. Several case reports document incidents of arterial air embolism from venous origin (paradoxical air embolism), where no intracardiac connections were demonstrated [1, 2]. Others have suggested that venous air emboli can cross the pulmonary circulation if the volume and rate of infusion are greater than a certain critical quantity [3, 4]. Although the mechanism of pulmonary filtration of venous air emboli is uncertain, it has been demonstrated that certain drugs, changes in inspired oxygen tension or the composition of the gas infused, may compromise this function [3, 5, 6]. Once bubbles are trapped in the lungs, elimination occurs primarily via the alveoli and, to a lesser degree, gas is taken up by the blood and adjacent tissues. Verstappen, Bernards and Kreuzer [7] described a steady state where the continued infusion of venous air was matched by alveolar excretion at a rate largely dependent upon pulmonary artery pressure; however, the passage of some bubbles through the pulmonary circulation was also considered possible. The effect of various inhalation anaesthetic agents (for example halothane or isoflurane) that have the ability to alter pulmonary vascular tone on the pulmonary filtering mechanism is uncertain [8].

The purpose of this study in dogs was to compare the effects of pentobarbitone, halothane and isoflurane anaesthesia on the ability of the pulmonary circulation to filter air emboli.

MATERIALS AND METHODS

Mongrel dogs were divided into three study groups to receive pentobarbitone, halothane or isoflurane anaesthesia. In group 1 anaesthesia was induced with pentobarbitone 30 ml kg^{-1} i.v.

JEFFREY KATZ, M.B., CH.B.; BASIL C. LEIMAN, M.B., B.CH.; BRUCE D. BUTLER, PH.D.; Department of Anesthesiology, The University of Texas Medical School at Houston, 6431 Fannin, MSMB 5.020, Houston, Texas 77030, U.S.A. Accepted for Publication: November 24, 1987.

Correspondence to J.K.

and maintained with pentobarbitone 10 mg kg^{-1} h^{-1}. In the dogs in groups 2 and 3 anaesthesia was induced with thiopentone 25 mg kg^{-1}, the trachea was intubated and the lungs ventilated (volume-cycled ventilator (Harvard)) with oxygen or room air ($F_{I_{O_2}}$ = 0.20–0.30). Ventilation was adjusted to 8–10 b.p.m. and a volume of 15–20 ml kg^{-1} to achieve Pa_{CO_2} of 4.67–5.32 kPa during the baseline period and was unchanged throughout the experiment. Anaesthesia was maintained with 1–1.5% halothane in group 2 and with 2–2.5% isoflurane in group 3.

Cannulae were placed in the abdominal aorta via the left femoral artery for measurement of mean arterial pressure (MAP), in the pulmonary artery via the left jugular vein for measurement of mean pulmonary artery pressure (PAP) and in the left ventricle via the right carotid artery to measure left ventricular end-diastolic pressure (LVEDP). The right femoral vein was cannulated to provide venous access. The cannulae were connected to strain gauge transducers (Statham P23ID), referenced at the level of the right atrium and calibrated with a mercury column. Cardiac output (CO) was measured in triplicate using the thermodilution technique (Instrumentation Laboratories 701). Pulmonary vascular resistance (PVR) was calculated as (PAP − LVEDP)/CO. Baseline data were collected after a 30-min period to allow stabilization.

The animals from each group were divided into three subgroups depending upon the rate of infusion of air. Room air was infused into the right atrium through the proximal lumen of the pulmonary artery catheter for 30 min using a reciprocating servo pump (Harvard). The infusion rates were 0.25, 0.30 and 0.35 ml kg^{-1} min^{-1}. No animal received more than one 30-min infusion of air. Total volumes of air infused were 162 ± 20 (0.25 ml kg^{-1} min^{-1}), 197 ± 37 (0.30 ml kg^{-1} min^{-1}) and 235 ± 53 (0.35 ml kg^{-1} min^{-1}). The size of the bubbles infused was approximately 500 μm in diameter.

Venous bubbles that crossed the pulmonary circulation were detected with a Doppler probe (9 mHz, Parks) positioned directly over the suprarenal aorta following laparotomy. The probe was suspended with bar clamps independent of the surgical cradle to avoid artefacts from gross movement. The received signals were filtered and amplified for analogue recording (Gould) and audio detection. Probe placement was verified by rapidly infusing physiological saline 10 ml into the left ventricular catheter and detecting the reflected change in the analogue signal.

Those animals in which arterial bubbles were detected had a left thoracotomy performed between the 5th and 6th ribs to permit direct examination of the superficial coronary vessels for the presence or absence of bubbles. The thoracotomy was performed at the end of the 30-min infusion period and the animals were monitored for an additional 60-min recovery period. At the end of the experiment, animals with detected bubbles were killed with potassium chloride (saturated) and their hearts examined for septal defects. If defects were found, the animal was excluded from the study.

Statistics. The incidence of arterial air embolism (table I) was compared using Fisher's Exact test. The data in tables II and III are means ± SEM. The data were analysed using a two-factor analysis of variance using Tukey's test of mulitple comparison.

RESULTS

The Doppler data demonstrating the incidence of spillover of venous air emboli into the arteries are shown in table I. At the lowest air infusion rate (0.25 ml kg^{-1} min^{-1}), arterial bubbles were not detected in the pentobarbitone- or halothane-anaesthetized dogs, but were detected in two of the nine receiving isoflurane anaesthesia. With the 0.30-ml kg^{-1} min^{-1} rate, spillover occurred in one dog receiving pentobarbitone, four given halothane, and two isoflurane-anaesthetized dogs. At the highest rate (0.35 ml kg^{-1} min^{-1}), the incidence of spillover was four with pentobarbitone, five with halothane and three for isoflurane-anaesthetized dogs. Within group comparisons were significant for pentobarbitone (0.25 ml kg^{-1} min^{-1} *v*. 0.35 ml kg^{-1} min^{-1}) and with halothane, comparing the 0.25 ml kg^{-1} min^{-1} rate with the 0.30- and 0.35-ml kg^{-1} min^{-1} rates. No differences

TABLE I. *No. animals (out of nine in each group) with Doppler-detected arterial bubbles.* †, *$P < 0.05$ *for pairs in same column*

Air dose (ml kg^{-1} ml^{-1})	Pentobarbitone	Isoflurane	Halothane	Totals
0.25	0*	2	0*†	2*
0.30	1	2	4*	7
0.35	4*	3	5†	12*
Totals	5	7	9	

TABLE II. *Cardiovascular data (means ± SEM). MAP = mean arterial pressure; CO = cardiac output; LVEDP = left ventricular end-diastolic pressure*

Air dose ($\text{ml kg}^{-1}\ \text{min}^{-1}$)	MAP (mm Hg)			CO (litre min^{-1})			LVEDP (mm Hg)		
	Baseline	Air	Recovery	Baseline	Air	Recovery	Baseline	Air	Recovery
Pentobarbitone									
0.25	115±4	101±3	112±5	2.6±0.4	2.2±0.2	2.4±0.3	1.5±0.4	3.4±0.6	1.3±0.3
0.30	123±5	98±7	122±5	2.5±0.3	2.4±0.3	2.6±0.3	3.4±0.3	4.0±0.3	3.2±0.3
0.35	129±4	103±5	125±4	3.0±0.2	2.2±0.2	2.6±0.3	3.0±0.3	3.0±0.3	3.2±0.3
Halothane									
0.25	98±5	81±5	85±3	2.0±0.2	2.2±0.2	1.9±0.2	5.8±0.6	5.7±0.5	6.2±0.5
0.30	110±4	66±10	79±7	2.2±0.2	2.4±0.6	2.3±0.6	5.2±0.6	4.6±0.7	5.5±1.2
0.35	96±5	68±9	83±7	2.4±0.4	2.4±0.4	2.2±0.2	5.6±0.4	4.9±0.6	4.5±0.8
Isoflurane									
0.25	120±6	94±8	99±6	3.0±0.1	3.2±0.3	3.4±0.3	3.2±0.3	4.3±0.4	3.1±0.3
0.30	130±5	98±8	99±4	3.3±0.4	3.3±0.5	2.9±0.4	4.7±0.5	4.2±0.4	4.5±0.5
0.35	122±6	91±7	98±7	3.1±0.2	3.5±0.3	2.7±0.3	4.2±0.4	4.8±0.4	3.9±0.3

TABLE III. *Pulmonary haemodynamic data (mean ± SEM). PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance.* n = *9 for each air dose group, 27 for each agent*

Air dose ($\text{ml kg}^{-1}\ \text{min}^{-1}$)	PAP (mm Hg)			PVR (dyne s cm^{-5})		
	Baseline	Air	Recovery	Baseline	Air	Recovery
Pentobarbitone						
0.25	14±1.3	31±1.5	15±0.8	256±45	761±48	183±41
0.30	13±1.2	34±2.8	13±0.8	226±36	1294±429	464±191
0.35	14±1.3	37±1.4	16±1.4	272±33	1125±78	280±18
Halothane						
0.25	13±1.0	31±1.8	14±0.6	283±36	971±82	340±39
0.30	12±0.9	29±1.1	13±1.2	265±47	1076±182	358±75
0.35	13±1.0	30±1.4	13±5.2	216±28	933±175	261±52
Isoflurane						
0.25	12±0.8	33±1.3	11±0.9	224±21	733±82	205±30
0.30	12±0.7	31±1.3	12±0.9	172±21	732±99	245±44
0.35	11±1.0	31±1.8	11±1.0	183±25	652±87	263±55

TABLE IV. *Statistical summary.* $^*P < 0.05$. *VAE = Venous air embolism; P = pentobarbitone; H = halothane; I = isoflurane; ns = not significant*

	VAE (A)	Anaesthetic agent (B)	A/B interaction	Air dose: individual comparison*	Agent: individual comparison*
PAP	0.001	0.002	0.01	Baseline *v.* 0.25*, 0.30*, 0.35*	P–I P–H
PVR	0.0001	0.002	0.04	Baseline *v.* 0.25*, 0.30*, 0.35*	P–I I–H
LVEDP	ns	0.001	ns	ns	P–H I–H
CO	ns	0.0001	ns	ns	P–I P–H I–H
MAP	0.0001	0.0001	ns	Baseline *v.* 0.25*, 0.30*, 0.35*	P–H I–H

were found between the various doses with isoflurane anaesthesia.

The haemodynamic responses to the venous air emboli are given in tables II and III. Statistical summaries are given in table IV. Mean arterial pressure decreased following the air in each group and with each anaesthetic agent. Following air, LVEDP and CO were unchanged with each dose of air; however, they were different when comparing the individual anaesthetic agents (table IV). PAP and PVR increased significantly following the embolization at each dose and for each agent. Further, there was a significant interaction between the amount of air administered and anaesthetic agent for both PAP ($P < 0.01$) and PVR ($P < 0.04$). The pentobarbitone-anaesthetized dogs demonstrated a higher response in PAP for 0.30 and 0.35 ml kg^{-1} min^{-1}. Arterial oxygen tensions decreased significantly following air for each anaesthetic group. Within-group comparisons were not different. In the pentobarbitone-anaesthetized dogs the mean (±SEM) Pa_{O_2} of the three doses decreased from 19.0±0.16 to 10.5±0.89 and the halothane and isoflurane values decreased from 16.0±0.89 to 7.7±0.31 and 20.0±0.69 to 10.9±0.41 kPa, respectively. The halothane Pa_{O_2} values following venous air emboli were lower than those of the other two groups. Arterial carbon dioxide tensions increased from 4.9±0.23 to 7.0±0.65, 4.7±0.16 to 6.9±0.29 and 5.1±0.12 kPa to 7.3±0.12 kPa, respectively, for the pentobarbitone, halothane and isoflurane anaesthetized dogs. The differences between the air dose groups or between the three anaesthetic agents were not significant.

DISCUSSION

The results of the present study demonstrate that the administration of air at rapid rates into the venous side of the circulation may be detected in the systemic arteries of dogs anaesthetized with pentobarbitone, isoflurane or halothane. The interpretation of the Doppler data in table I is particularly dependent upon the sensitivity of ultrasound to detect circulating bubbles. The use of Doppler is widespread for the detection of venous bubbles that can occur in association with neurosurgery or with decompression sickness [9]. The sensitivity of these devies has been shown to be reliable for detection of microbubbles as small as 14 μm diameter [10]. This sensitivity allows for accurate qualitative detection of circulating bubbles. Quantitative interpretations are limited as a result of artefactual interference that can occur with coincident counting or misalignment of the incident beam with the bubbles [11, 12].

In the present study, Doppler was used to detect qualitatively the presence or absence of arterial bubbles following venous air embolism. With Doppler, the intensity of the reflected signal is related to the cross-sectional scattering area of the bubbles as well as the difference in density between the gas and the surrounding medium [13, 14]. The ultrasonic beam reflected from a gas bubble is, therefore, of an intensity several orders of magnitude greater than some more dense particles (for example glass beads, cellular aggregates or plastic spheres) [14, 15].

In previous studies we have demonstrated that venous air emboli do not normally reach the systemic circulation since they are filtered in the lungs [5]. The limit to this filtration can be exceeded when the lungs are challenged with air emboli administered at rates greater than 0.30 ml kg^{-1} min^{-1} [4] for dogs and at 0.15 ml kg^{-1} min^{-1} for unanaesthetized sheep receiving nitrogen bubbles [3]. The consequences of an embolism crossing the lungs is dependent upon the target organ in which the bubbles ultimately become trapped. Air in the coronary arteries can reduce myocardial contractility secondary to ischaemia which may lead to cardiac arrest [16]. Goldfarb and Bahnson [17] observed myocardial ischaemia in dogs receiving as little as 0.05 ml of air directly into the left coronary artery, while 0.5–1 ml of air injected into the left heart can be fatal [18].

The consequences of cerebral air embolism are often more diffuse if gross motor or behavioural changes are not immediately apparent. Additionally, with anaesthetized patients, any cerebral symptoms may go unnoticed until the postoperative period, although some cardiovascular symptoms have been shown to occur in cats even while they are under anaesthesia [19]. Other cases have been reported of fatal cerebral air embolism resulting from amounts of air as small as 2–3 ml [20]. The source of coronary or cerebral air may include venous air emboli that cross to the systemic circulation via the pulmonary microcirculation, through pulmonary arteriovenous shunts or via an atrial septal defect (ASD) [21]. In the present study we excluded those dogs demonstrating arterial bubbles in which an ASD was detected at autopsy. The majority of clinical cases of paradoxical air embolism involve patients with an ASD, although case reports frequently describe incidents of venous air emboli that result in cerebral air embolism where no cardiac septal defect was found [1, 2, 22, 23].

Several factors may influence the passage of emboli across the lungs—the size of the bubble, surface tension and vascular pressure. The composition of the gas inside the bubble may also influence the size and rate of dissolution in the blood. This is more obvious with oxygen bubbles, since the oxygen tension in the arterial blood is less than that inside the bubble and dissolution is promoted by the disparity in the tensions. Bubbles of air or nitrogen will remain in the blood for longer periods of time, especially when the ventilatory gases resemble room air. This is because of similarity in the partial pressures of the gases inside the bubbles to those of the surrounding blood, as well as the solubility of nitrogen as compared with oxygen. These phenomena were described by Spencer and Oyama [3] who also reported that equivalent doses of oxygen or carbon dioxide venous emboli did not cross the lungs when compared with nitrogen bubbles.

Tonic factors affecting the diameter of pulmonary vessels (for example, anaesthetic agents, neurogenic or hypoxic pulmonary vasoconstriction, Pa_{CO_2} or endogenous mediators) that result from embolization may influence the passage of bubbles across the lungs. The pulmonary vasoconstrictor response to emboli has been attributed to a neurogenic reflex [24] acting in conjunction with mechanical blockage of vessels by bubbles. Further evidence suggests that mediators released in response to emboli (serotonin, histamine, kinins) may also affect vascular tone and vessel permeability [25, 26].

Mathers, Benumoff and Wahrenbrock [27] reported modest but significant decreases in PVR with halothane and isoflurane anaesthesia. The data in table III show baseline PVR values as not being different when comparing the three anaesthetic agents. Following venous air embolization, PVR increased with each agent and dose of air. Although the effects of the various anaesthetic effects on PVR are described, our data do not allow for specification of the particular vessel type involved in the pulmonary vascular filtration of gas emboli. The inhibition of hypoxic pulmonary vasoconstriction by isoflurane [28] or halothane [29] is unlikely in the present study as the Pa_{CO_2} values were likely to have been sufficient to avoid this reflex mechanism. Furthermore, alveolar hypoxia exerts a greater influence on those vessels at close proximity to the alveolar spaces [30], whereas the pulmonary artery hypoxaemia (low mixed venous oxygen tension) that occurred in this study has less of an influence on the overall pressor response and affects non-alveolar vessels to a greater degree [31]. Vasoconstriction may also occur in larger pulmonary vessels (300–500 μm) as a result of pulmonary artery hypercapnia [31], while the smaller vessels are influenced by the alveolar concentrations.

In summary, our findings confirm that air entering the venous circulation can cross to the systemic circulation via the lungs. We have also demonstrated that, in dogs anaesthetized with pentobarbitone or halothane, crossover is more likely to occur as the volume of air infused is increased. This claim does not apply to isoflurane-anaesthetized dogs. Although the incidence of paradoxical air embolism in the absence of cardiac defects is low, our results provide an explanation for these occurrences.

ACKNOWLEDGEMENTS

Supported in part by BRS Grant No. RR-05745-11, U.S. Public Health Service and American Society of Anesthesiologists Starter Grant.

The authors would like to thank Miss Sue Luehr for her technical assistance, Mrs Susan Laine for statistical assistance and Mrs Verna Jasso for preparing the manuscript.

REFERENCES

1. Marquez, J, Slader A, Gendell H, Boehnte M, Mendlow H. Paradoxical cerebral air embolism without an intracardiac defect. *Journal of Neurosurgery* 1981; 55: 997–1000.
2. Jacobsen WK, Briggs BA, Mason LJ. Paradoxical air embolism associated with a central total parenteral nutrition catheter. *Critical Care Medicine* 1983; 11: 388–389.
3. Spencer MP, Oyama P. Pulmonary capacity for dissipation of venous gas emboli. *Aerospace Medicine* 1971; 42: 822–827.
4. Butler BD, Hills BA. Transpulmonary passage of venous air emboli. *Journal of Applied Physiology* 1985; 59: 543–547.
5. Butler BD, Hills BA. The lung as a filter for microbubbles. *Journal of Applied Physiology* 1979; 47: 537–543.
6. Niden AH, Aviado DM. Effects of pulmonary embolism on the pulmonary circulation with special references to arteriovenous shunts in the lungs. *Circulation Research* 1956; 4: 67–73.
7. Verstappen FTV, Bernards JA, Kreuzer F. Effects of pulmonary gas embolism on circulation and respiration in the dog. III. Excretion of venous gas bubbles by the

lungs. *Pflugers Archiv. European Journal of Physiology* 1977; **370**: 67–70.

8. Drummond JC. Of venous air embolism, aminophylline and volatile agents. *Anesthesiology* 1984; **60**: 389.
9. Michenfelder JD, Miller RH, Gronert GA. Evaluation of an ultrasonic device (Doppler) for the diagnosis of venous air embolism. *Anesthesiology* 1972; **36**: 164–167.
10. Hills BA, Butler BD. A method of producing calibrated microbubbles for air embolism studies. *Journal of Applied Physiology* 1981; **51**: 524–528.
11. Butler BD. Biophysical aspects of gas bubbles in blood. *Medical Instrumentation* 1985; **19**: 59–62.
12. Furness A, Wright G. Microbubble detection during cardiopulmonary bypass for open heart surgery. *Life Support Systems* 1985; **3**: 103–109.
13. Medwin H. Counting bubbles acoustically: a review. *Ultrasonics* 1977; **15**: 7–13.
14. Lubbers J, Van Den Berg JW. An ultrasonic detector for micro gas emboli in a blood flow line. *Ultrasound in Medicine and Biology* 1977; **2**: 301–310.
15. Nishi RY. Ultrasonic detection of bubbles with doppler flow transducers. *Ultrasonics* 1972; **10**: 173–179.
16. Clayton DG, Evans P, Williams C, Thurlow AC. Paradoxical air embolism during neurosurgery. *Anesthesiology* 1985; **40**: 981–989.
17. Goldfarb D, Bahnson HT. Early and late effects on the heart of small amounts of air in the coronary circulation. *Journal of Thoracic and Cardiovascular Surgery* 1963; **46**: 368–378.
18. Stevenson HE. *Cardiac Arrest and Resuscitation*. St Louis: C.V. Mosby, 1974; 231–235.
19. Evans DE, Kobrine AI, Weathersby PK, Bradley ME. Cardiovascular effects of cerebral air embolism. *Stroke* 1981; **12**: 338–344.
20. Michel L, Poskanzer DC, McKusick KA, Nardi GL, Malt RA. Fatal paradoxical air embolism to the brain: Complication of central venous catheterization. *Journal of Parenteral and Enteral Nutrition* 1982; **6**: 68–70.
21. Perkins-Pearson NAK, Marshall WK, Bedford RF. Atrial pressures in the seated position. Implications for paradoxical air embolism. *Anesthesiology* 1982; **57**: 493–497.
22. Harrison GR. Paraxodical air embolus. *Anaesthesia* 1986; **41**: 763.
23. Furuya H, Okumura F. Detection of paradoxical air embolism by trans-esophageal echocardiography. *Anesthesiology* 1984; **60**: 374–377.
24. Lee BC, Van Der Zee H, Malik AB. Site of pulmonary edema after unilateral microembolization. *Journal of Applied Physiology*. 1979; **47**: 556–560.
25. Said SI. Release induced by physical and chemical stimuli. In: Bakhle YS, Vane JR, eds. *Metabolic Functions of the Lung*. New York: Dekker, 1977: 297–320.
26. Philp RB, Inwood MJ, Warren BA. Interactions between gas bubbles and components of the blood: implications in decompression sickness. *Aerospace Medicine* 1972; **43**: 946–953.
27. Mathers J, Benumof L, Wahrenbrock EA. General anesthetics and regional hypoxic pulmonary vasoconstriction. *Anesthesiology* 1977; **46**: 111–114.
28. Sykes MK, Gibbs JM, Loh L, Marin JBL, Obdrzalek J, Arnot RN. Preservation of the pulmonary vasoconstrictor response to alveolar hypoxia during the administration of halothane to dogs. *British Journal of Anaesthesia* 1978; **50**: 1185–1196.
29. Bjertnaes LJ. Hypoxia-induced pulmonary vasoconstriction in man: inhibition due to diethyl ether and halothane anaesthesia. *Acta Anaesthesiologica Scandinavica* 1978; **22**: 570–588.
30. Von Hayek H. *The Human Lung*. New York: Hafner, 1960: 245–252.
31. Bergofsky EH. Ion and membrane permeability in the regulation of the pulmonary circulation. In: Fishman AP, Hecht HH, eds. *The Pulmonary Circulation and Interstitial Space*. Chicago: University of Chicago Press, 1969; 269–286.

Br. J. Anaesth. (1988), **61**, 206–210

KETAMINE FAILS TO PROTECT AGAINST ISCHAEMIC NEURONAL NECROSIS IN THE RAT

M. L. JENSEN AND R. N. AUER

SUMMARY

Ketamine is a dissociative anaesthetic known to be an N-methyl-D-aspartate receptor blocker. Since the NMDA excitatory receptor on neurones is implicated in ischaemic neuronal necrosis, ketamine might be expected to have a beneficial effect in cerebral hypoxia–ischaemia. Ketamine was tested in a rat model of forebrain ischaemia allowing 7 days recovery. Ketamine 6 mg kg^{-1} i.v. was administered 5–10 min before ischaemia in one group of rats, and ketamine 60 mg kg^{-1} day^{-1} i.m. for 3 days and 7 continuous days after ischaemia in two other groups. An additional group received ketamine 24 mg kg^{-1} i.v. before ischaemia and 120 mg kg^{-1} day^{-1} i.m. after ischaemia for 7 days continuously. Control rats received ischaemia but no treatment. The results were compared with untreated controls by neuropathological examination of the entire brain, sectioned subserially. There was no significant difference in necrosis between treated and untreated groups after any of the ketamine regimens. The findings demonstrate that systemically administered ketamine fails to protect the brain against hypoxic–ischaemic injury in the rat.

Ketamine has been in clinical use for more than two decades. In recent years it has become clear that, in addition to its effect as a dissociative anaesthetic, ketamine is an effective blocker of NMDA excitatory amino acid receptors in the brain [1–4]. The NMDA receptor has been implicated as the subtype of excitatory amino acid receptor responsible for neuronal necrosis in hypoxia–ischaemia [5, 6]. As ketamine protects hippocampal neurones from anoxia *in vitro*, and as this agent crosses the blood–brain barrier when administered systemically, we have investigated the potential usefulness of ketamine in preventing ischaemia-induced neuronal degeneration and death.

MATERIALS AND METHODS

Ischaemia was induced in male Wistar rats by a modification of the model developed by Smith and co-workers [7]. Briefly, forebrain ischaemia was induced by a combination of carotid clamping and hypotension. The rats were anaesthetized in 3% halothane, the trachea intubated, and the lungs ventilated using a Starling type ventilator, with 66% nitrous oxide and 0.7% halothane in oxygen. A tail vein was cannulated and a continuous infusion of suxamethonium 2 mg h^{-1} was administered to maintain continuous paralysis. A tail artery was cannulated and arterial pressure was recorded continuously using a Statham transducer (Gould P50, Oxnard, Calif.). Arterial pressure recordings were digitized every 6 s and recorded on a computer hard disk. These readings were used later to calculate the mean intra-ischaemic arterial pressures in the various groups (table I). A central venous catheter was inserted via the right jugular vein and attached to a pre-warmed 10-ml heparinized syringe.

After a period of stabilization of approximately 30 min, the rats were given trimetaphan 5 mg kg^{-1} i.v. The rats were exsanguinated into the pre-warmed heparinized syringe. When arterial pressure reached 50 mm Hg, two clamps were placed around the carotid arteries. Arterial pressure was maintained at 50 mm Hg by withdrawal and reinfusion of blood via the central venous catheter.

M. L. JENSEN, B.SC.; R. N. AUER*, M.D., PH.D., F.R.C.P.; Departments of Pathology and Clinical Neurosciences, University of Calgary, Calgary, Alberta, Canada. Accepted for Publication: November 28, 1987.

*Address for correspondence: Neuropathology, Health Sciences Center, 3330 Hospital Drive NW, Calgary, Alberta, Canada T2N 4N1.

TABLE I. *Dosage of ketamine and physiological variables for each group (mean ± SEM). Number of injections received per day – group 3 : 2 (two rats) or 3 (four rats) ; group 4 : 2 (four rats) or 4 (two rats) ; group 5 : 2 (all in group). *Average of readings sampled every 6 s over entire ischaemic period. †Duration with both carotids clamped and AP ⩽ 50 mm Hg*

	Group 1	Group 2	Group 3	Group 4	Group 5
n	8	6	6	6	6
Survival (days)	7	7	7	7	7
Ketamine (mg kg^{-1})					
Before ischaemia	—	6 i.v.	—	—	24
After ischaemia					
I.v. < 45 min post-ischaemia	—	—	18	18	72
I.m. dose per day	—	—	60	60	60
No. of days ketamine post-ischaemia			3	7	7
AP before ischaemia (mm Hg)	123±2	118±3	125±4	115±3	120±3
Mean intra-ischaemic AP* (mm Hg)	49.5±0.2	47.5±0.3	50.3±0.2	48.5±0.3	47.3±0.2
Mean ischaemic duration† (min : s)	9:13±0:02	9:07±0:02	9:13±0:02	9:09±0:02	9:05±0:02
AP after ischaemia (mm Hg)	128±3	125±4	133±3	118±2	121±2
Glucose (mmol litre^{-1})					
Before ischaemia	7.8±0.9	6.9±0.7	7.9±0.5	6.5±0.4	9.5±0.5
After ischaemia	10.8±0.9	6.9±0.7	12.4±1.1	10.5±1.2	9.1±1.2
$P\text{co}_2$ (kPa)					
Before ischaemia	4.51±0.15	4.6±0.19	4.76±0.2	4.49±0.19	4.59±0.15
After ischaemia	5.31±0.19	5.11±0.24	4.76±0.33	4.94±0.13	4.71±0.15
$P\text{o}_2$ (kPa)					
Before ischaemia	17.52±1.28	14.69±1.16	13.82±1.09	16.04±1.2	16.63±0.91
After ischaemia	17.15±1.16	15.7±1.69	16.23±1.43	17.31±1.71	17.37±1.29
pH					
Before ischaemia	7.415±0.018	7.425±0.017	7.389±0.016	7.396±0.012	7.410±0.018
After ischaemia	7.334±0.013	7.388±0.023	7.391±0.023	7.358±0.012	7.369±0.020

After 9 min of ischaemia, the carotid clamps were released and blood reinfused. The trachea was extubated and the animal allowed to awaken, to survive for 1 week.

The schedules, doses and routes of administration of ketamine are given for each group in table I.

A subgroup of two of the six rats receiving ketamine for 7 days (group 4) received 60 mg kg^{-1} day^{-1} in four divided doses rather than two divided doses in order to test for possible lack of efficacy resulting from decreasing blood concentrations of ketamine between insufficiently frequent doses of drug.

All rats were sacrificed 1 week after ischaemia. Rats were re-anaesthetized with 2–3 % halothane and the trachea intubated. A thoracotomy was performed, and trans-cardiac perfusion was carried out using 4 % formaldehyde, phosphate-buffered to pH 7.35.

Brains were removed the following day, processed in graded ethanols and xylol, and embedded in paraffin. Subserial sectioning was performed in order to obtain sections from the cerebral cortex, hippocampus, caudate nucleus, diencephalon, brain stem and cerebellum in all animals.

TABLE II. *Extent of neuronal necrosis in the hippocampus, CA1 region. Differences not significant (Student* t *test)*

	No. cells dead	Total No. cells	% Cells necrotic
Group 1	8326	12405	67
Group 2	5316	11762	45
Group 3	5583	8263	68
Group 4	8224	13979	59
Group 5	7597	14276	53

Sections were double stained with 1 % acid fuchsin and 0.1 % cresyl violet, and the number of acidophilic neurones, previously shown to be necrotic [8], was counted under light microscopy.

Integers representing the degree of neuronal necrosis were assigned for the cerebral cortex and striatum, the main telencephalic brain regions vulnerable to ischaemic damage, as follows: in the hippocampus, where total cell counts were available from previous quantitative studies [9], necrotic neurones were visually counted directly and given a percentage (table II). In the cerebral cortex, where total cell counts were unavailable, 10–100 necrotic cells per section were assigned the integer 1, 100–1000 necrotic neurones were given 2, and greater than 1000 necrotic neurones

TABLE III. *Damage scores (mean ± SEM) in each group for cells of the neocortex. See text for details of scoring*

Group 1	2.5±0.5
Group 2	2.5±0.3
Group 3	2.3±0.4
Group 4	2.2±0.4
Group 5	2.0±0.5

3. The scores for both sides of the brain were summed to give the regional damage index for cerebral cortex (table III).

RESULTS

Clinical observations

Control rats (group 1) subjected to 9 min of ischaemia showed normal grooming and eating behaviour 24 h after surgery.

Rats given pre-ischaemic ketamine (group 2) showed no delay in awakening after operation and were indistinguishable from control rats.

Rats given post-ischaemic ketamine (groups 3, 4 and 5) could be weaned from the ventilator in 2–2.5 h, in contrast to rats in groups 1 and 2, where tracheal extubation was possible after 30 min. For the duration of time during which they received ketamine injections, post-ischaemic rats in these three groups were in a clinically dissociated, sluggish state and reacted minimally to repeated i.m. injections of ketamine. This was taken to reflect adequate central effect of the drug.

Neuropathology

Ischaemia produced the well-described acidophilic neuronal change in cerebral cortex and hippocampus [10]. Acidophilic neurones showed blurring of the cytoplasmic organelles including the Nissl substance, and a loss of nuclear detail. Macrophages were occasionally present, and this was not used as a criterion for neuronal necrosis. The cardinal criterion used was the intense cytoplasmic acidophilia [8, 9] which was either present or absent.

No significant difference in neuronal necrosis was seen in the ketamine pretreated group, the pre- and post-treated group, or in the two groups receiving 3 and 7 days of post-ischaemic ketamine (tables II, III).

Damage was seen consistently in the GABA-ergic lateral reticular nucleus of the thalamus, as described previously [10]. The caudate nucleus was examined in all rats, but was not affected in any animals. One animal in group 1 and one in group 4 showed tectal infarcts in the inferior colliculi, but the characteristic audiogenic running seizures, seen after ischaemia in rats (Voll and Auer, in preparation) were not present after this relatively short duration of ischaemia. Cerebellar damage was uniformly absent.

DISCUSSION

The present findings demonstrate that ketamine, a centrally acting potent NMDA receptor blocker [4], is not effective in preventing ischaemic neuronal necrosis in the rat brain.

Ketamine acts at the NMDA receptor by non-competitive antagonism, at an allosteric site distinct from the ion channel [11]. Numerous *in vitro* studies based on cell culture or tissue slice preparations have demonstrated the effectiveness of ketamine in blocking NMDA mediated excitatory responses [1–3, 12–16].

The NMDA subtype of excitatory amino acid receptor has been implicated in neuronal necrosis produced by hypoxia–ischaemia [17]. Based on these findings, and on a protective effect of ketamine against hypoxia seen in cultured cortical neurones [18, 19] and in the hippocampal slice [19], a beneficial effect might be suspected *in vivo*.

Ketamine has been shown to be effective in preventing neuronal excitotoxicity *in vivo* produced by NMDA excitatory receptor agonists. Systemic injection of ketamine 30 mg kg^{-1} i.p. and pentobarbitone 36 mg kg^{-1} i.p., 30 min before intra-hippocampal injections of either quinolinic acid (120 μmol) or NMDA (50 μmol) resulted in partial protection of hippocampal neurones [20].

In view of these properties of ketamine as an NMDA receptor antagonist, and of its demonstrated *in vivo* protective action against toxicity from NMDA agonists [20], the failure of ketamine to protect against ischaemic neuronal necrosis may seem surprising in the light of mounting evidence that glutamate release and NMDA receptor activation are involved in hypoxic–ischaemic neuronal death [21]. The clinically dissociated state of the animals seen after ketamine administration would seem to indicate adequate penetration of the brain by the drug. Even in the CA1 zone of the hippocampus, where NMDA receptor sites are concentrated [22, 23], no beneficial effect was seen in protecting selectively vulnerable neurones. Hence, it appears as though the *in vivo* testing for prevention of neuronal necrosis in a whole animal ischaemia model constitutes a more stringent criterion than *in vitro* testing for drugs reported to be effective against hypoxia–ischaemia in tissue culture and slice preparations [1–3, 12–15, 24]. It may be that only NMDA antagonists of even higher potency than ketamine, such as MK-801 [25] may be effective in preventing ischaemic neuronal death [26, 27].

Ketamine is known to activate cholinergically mediated cerebral vasodilatation, causing an increase in cerebral blood flow (CBF), and increased intracranial pressure [28, 29]. One might presume that any increase in post-ischaemic CBF would have been of benefit in the present study.

Few studies have examined the effect of ketamine in cerebral ischaemia. One research group found that ketamine anaesthesia increased stroke-related mortality in gerbils [30]. We were unable to confirm a detrimental effect on mortality in the rat. Another study in the gerbil demonstrated aggravation of infarction by ketamine [31]. The present study was designed to study the effect of ketamine only on selective neuronal necrosis and a 9-min period of cerebral ischaemia was chosen for that purpose. Therefore, any effect on infarction seen after higher dose ischaemic insult cannot be determined from the present findings.

Application of excitatory amino acid blockers in clinical situations should be based ideally on a demonstrated beneficial effect on both brain structure and function in animals. The present study demonstrated neither aggravation nor mitigation of the clinical or neuropathological sequelae of transient cerebral ischaemia. Thus, it seems likely that ketamine is neither harmful nor beneficial in clinical situations which may cause cerebral ischaemia.

ACKNOWLEDGEMENTS

This work was supported by the Alberta Heritage Foundation for Medical Research, the Foothills Hospital Research and Development Fund, and the Medical Research Council of Canada (grant No. MA-9935).

REFERENCES

1. Anis NA, Berry SC, Burton NR, Lodge D. The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurones by N-methyl-aspartate. *British Journal of Pharmacology* 1983; **79**: 565–575.
2. Martin D, Lodge D. Ketamine acts as non-competitive N-methyl-D-aspartate antagonist on frog spinal cord *in vitro*. *Neuropharmacology* 1985; **24**: 999–1003.
3. Thomson AM, West DC, Lodge D. An N-methyl-aspartate receptor-mediated synapse in rat cerebral cortex: a site of action of ketamine? *Nature* (*London*) 1985; **313**: 479–481.
4. Olney JW, Price MT, Fuller TA, Labruyere J, Samson L, Carpenter M, Mahan K. The anti-excitotoxic effects of certain anesthetics, analgesics and sedative-hypnotics. *Neuroscience Letters* 1986; **68**: 29–34.
5. Rothman SM. Synaptic activity mediates death of hypoxic neurones. *Science* 1983; **220**: 536–537.
6. Simon RP, Swan JH, Griffiths T, Meldrum BS. Blockade of N-methyl-D-aspartate receptors may protect against ischemic damage in the brain. *Science* 1984; **226**: 850–852.
7. Smith M-L, Bendek G, Dahlgren N, Rosén I, Wieloch T, Siesjö BK. Models for studying long-term recovery following forebrain ischemia in the rat. 2. A 2-vessel occlusion model. *Acta Neurologica Scandinavica* 1984; **69**: 385–401.
8. Auer RN, Kalimo H, Olsson Y, Siesjö BK. The temporal evolution of hypoglycaemic brain damage. I. Light and electron microscopic findings in the rat cerebral cortex. *Acta Neuropathologica* (*Berlin*) 1985; **67**: 13–24.
9. Auer RN, Olsson Y, Siesjö BK. Hypoglycemic brain injury in the rat. Correlation of density of brain damage with the EEG isoelectric time: A quantitative study. *Diabetes* 1984; **33**: 1090–1098.
10. Smith M-L, Auer RN, Siesjö BK. The density and distribution of ischemic brain injury in the rat after 2–10 min of forebrain ischemia. *Acta Neuropathologica* (*Berlin*) 1984; **64**: 319–332.
11. Kemp JA, Foster AC, Wong EHF. Non-competitive antagonists of excitatory amino acids. *Trends in Neurosciences* 1987; **10**: 294–298.
12. Lodge D, Anis NA, Burton NR. Effects of optical isomers of ketamine on excitation of cat and rat spinal neurones by amino acids and acetylcholine. *Neuroscience Letters* 1982; **29**: 281–286.
13. Duchen MR, Burton NR, Biscoe TJ. An intracellular study of the interactions of N-methyl-DL-aspartate with ketamine in the mouse hippocampal slice. *Brain Research* 1985; **342**: 149–153.
14. Honey CR, Miljkovic Z, MacDonald JF. Ketamine and phencyclidine cause a voltage-dependent block of responses to L-aspartic acid. *Neuroscience Letters* 1985; **61**: 135–139.
15. Thomson AM. Comparison of responses to transmitter candidates at an N-methylaspartate receptor mediated synapse, in slices of rat cerebral cortex. *Neuroscience* 1986; **17**: 37–47.
16. MacDonald JF, Miljkovic Z, Pennefather P. Use-dependent block of excitatory amino acid currents in cultured neurons by ketamine. *Journal of Neurophysiology* 1987; **58**: 251–266.
17. Simon RP, Griffiths T, Evans MC, Swan JH, Meldrum BS. Calcium overload in selectively vulnerable neurones in the hippocampus during and after ischemia: An electron microscopy study in the rat. *Journal of Cerebral Blood Flow and Metabolism* 1984; **4**: 350–361.
18. Weiss J, Goldberg MP, Choi DW. Ketamine protects cultured neocortical neurons from hypoxic injury. *Brain Research* 1986: **380**: 186–190.

19. Rothman SM, Thurston JH, Hauhart RE, Clark GD, Solomon JS. Ketamine protects hippocampal neurons from anoxia *in vitro*. *Neuroscience* 1987; **21**: 673–678.
20. Lees GJ. Effects of ketamine on the *in vivo* toxicity of quinolinate and N-methyl-D-aspartate in the rat hippocampus. *Neuroscience Letters* 1987; **78**: 180–186.
21. Rothman SM, Olney JW. Glutamate and the pathophysiology of hypoxic/ischemic brain damage. *Annals of Neurology* 1986; **19**: 105–111.
22. Monaghan DT, Holets VR, Toy DW, Cotman CW. Anatomical distributions of four pharmacologically distinct ^{3}H-L-glutamate binding sites. *Nature* (*London*) 1983; **306**: 176–179.
23. Greenamyre JT, Olson JMM, Penney JB jr, Young AB. Autoradiographic characterization of N-methyl-d-aspartate-quisqualate- and kainate-sensitive glutamate binding sites. *Journal of Pharmacology and Experimental Therapeutics* 1985; **233**: 254–263.
24. Bendo AA, Kass IS, Cottrell JE. Anesthetic protection against anoxic damage in the rat hippocampal slice. *Brain Research* 1987; **403**: 136–141.
25. Rothman SM, Olney JW. Excitotoxicity and the NMDA receptor. *Trends in Neurosciences* 1987; **10**: 299–302.
26. Gill R, Foster C, Woodruff GN. Systemic administration of MK-801 protects against ischemia-induced hippocampal neurodegeneration in the gerbil. *Journal of Neuroscience* 1987; **7**: 3343–3349.
27. McDonald JW, Silverstein FS, Johnston MV. MK-801 protects the neonatal brain from hypoxic–ischemic damage. *European Journal of Pharmacology* 1987; **140**: 359–361.
28. Oren RE, Rasool NA, Rubinstein EH. Effect of ketamine on cerebral cortical blood flow and metabolism in rabbits. *Stroke* 1987; **18**: 441–444.
29. Reicher D, Bhalla P, Rubinstein EH. Cholinergic cerebral vasodilator effect of ketamine in rabbits. *Stroke* 1987; **18**: 445–449.
30. Christie-Pope BC, Palmer GC, Poulakos L, Medina MA, Callahan AS III, Palmer SJ. Regional cyclic AMP systems during secondary ischemia in gerbils: Influence of anesthetic agents. *Experimental Neurology* 1984; **84**: 494–511.
31. Lightfoote WE, Molinari GF, Chase TN. Modification of cerebral ischemic damage by anesthetics. *Stroke* 1977; **8**: 627–628.

Br. J. Anaesth. (1988), **61**, 211–216

PREDICTING DIFFICULT INTUBATION

M. E. WILSON, D. SPIEGELHALTER, J. A. ROBERTSON AND P. LESSER

SUMMARY

The amount of larynx seen at intubation was assessed in 633 adult patients undergoing routine surgery. Various measurements of the head and neck were made in an attempt to discover which features were associated with difficulty with laryngoscopy (defined as the inability to see even the arytenoids). In addition 38 patients, reported by colleagues because they had been "difficult to intubate", were measured. Five useful risk factors, measured at three levels of severity, were identified. A simple predictive rule was developed and tested on a prospective set of 778 patients, in 1.5% of whom laryngoscopy was found to be difficult. Depending on the threshold chosen, the rule allowed the detection of, for example, 75% of the "difficult" laryngoscopies at a cost of falsely identifying 12% of the "not difficult" patients.

A common cause of mortality and morbidity attributable to anaesthesia is difficult or failed intubation. If those patients in whom intubation proves difficult could be identified in advance, it could be arranged that a senior anaesthetist, properly equipped to deal with the problem, could be present. Many features that are believed to indicate difficulty of intubation have been described [1], but a predictive rule that is useful in routine clinical practice has not been formulated as yet and properly evaluated. Our study was designed to collect data, develop a rule and test it. It was considered that failure to intubate would be a poor criterion for a study, since complete failure is a very rare event. Moreover, the difficulty of intubation is influenced by factors other than anatomical ones, for example, the anaesthetist's skill and persistence. Therefore, the difficulty of laryngoscopy, that is, the amount of larynx seen on laryngoscopy, was studied.

PATIENTS AND METHODS

First, a consecutive series of patients, and some additional patients in whom the trachea was known to be difficult to intubate, were measured to establish descriptive statistics so that a simple rule could be developed. Next, this rule was tested on the data from which it was derived and found to be satisfactory. Finally, the rule was tested prospectively on a further group of patients.

Initial study

Data were collected from a total of 633 patients older than 16 years of age undergoing non-emergency surgery at a District General Hospital and Royal Naval Hospital. During the periods of collection consecutive series of patients, who represented the daily work load of one consultant and three registrars, were recruited to the study. A number of measurements and assessments of features that might predict difficult intubation were made on each patient. These features were:

Inter-incisor gap (IG), measured with the mouth fully open; mandibular length (ML) (tempero–mandibular joint to the tip of the lower incisors); anterior mandibular depth (AM) (base of lower incisor to bottom of chin); posterior mandibular depth (PMD) (depth of mandible measured through the skin immediately posterior to the third molar); neck length (NL) (measured

---

MICHAEL E. WILSON, PH.D., F.F.A.R.C.S; PIERS LESSER†, F.F.A.R.C.S; Department of Anaesthesia, Royal United Hospital, Bath BA1 3NG. DAVID SPIEGELHALTER, PH.D., MRC Biostatistics Unit, 5 Shaftesbury Road, Cambridge CB2 2BW. J. ALEXANDER ROBERTSON*, F.F.A.R.C.S., Royal Naval Hospital, Plymouth. Accepted for Publication: February 27, 1987.

Present addresses:

†Department of Anaesthesia, The General Infirmary at Leeds, Leeds.

*Department of Anaesthesia, Airedale District General Hospital, Steeton, Nr Keighley, Yorks.

Correspondence to M. E. W.

TABLE I. *Definitions of the different grades of difficult laryngoscopy with the number and percentage of patients found in each grade for the initial series (with and without pressure applied to the larynx) and for the prospective series (with pressure applied)*

Difficulty		Initial series		Prospective series
Grade	Amount of larynx seen	No laryngeal pressure	With laryngeal pressure	With laryngeal pressure
1	Almost all of cords	248 (57.5%)	153 (75.7%)	636 (81.7%)
2	Only half of cords	97 (22.5%)	24 (11.9%)	101 (13.0%)
3	Only arytenoids	46 (10.7%)	13 (6.4%)	29 (3.7%)
4	Only epiglottis	39 (9.0%)	11 (5.4%)	10 (1.3%)
5	Not even epiglottis	1 (0.2%)	1 (0.5%)	2 (0.3%)
Totals		431	202	778

with the head in the intubating position, from tip of mastoid process to the medial end of the clavicle); neck circumference (NC); subluxation (SLux) (maximal forward protrusion of the lower incisors beyond the upper incisors); portion of mandible anterior to a line drawn from the tip of the upper incisors to the cricoid with the head in the intubating position (A); portion of mandible posterior to a line drawn from the tip of the upper incisors to the cricoid with the head in the intubating position (B); distance between sternal notch and cricoid with head in the intubating position (SC); with the head in the intubating position, the mid-point between the suprasternal notch and the tip of the chin is marked. The position of the cricoid is measured in relation to this mark (L); maximum range of head and neck flexion (HFNF) measured from the neutral erect position; maximum range of head and neck extension (HENE) measured from the neutral erect position; maximum range of head and neck movement (HFNF+HENE).

Initially, head and neck movement was measured with a special protractor. However, when it became clear that a simpler procedure was adequate, this was adopted. For this, the patient was asked to extend fully the head and neck while a pencil was stood vertically on the forehead. The orientation of the pencil was adjusted so that it was parallel to a distant window frame. Then, while the pencil was held firmly in position, the head and neck were fully flexed and the pencil was sighted against the horizontal of the window frame to judge if it had moved through 90°.

The severity of receding mandible or long upper incisors (buck teeth) was estimated on a subjective three-point scale (0 = normal; 1 = moderate; 2 = severe). The reliability of these scales was confirmed with a series of photographs. Agreement was good, and the chance that a second colleague would agree with the assessment of a first colleague was at least 70%.

The difficulty of laryngoscopy was assessed at intubation. With the head in the optimum position, a Macintosh laryngoscope bearing a standard blade was inserted into the throat and the proportion of the laryngeal aperture seen was recorded on the 1–5 scale defined in table I.

In the initial study the difficulty of laryngoscopy was estimated in 202 patients with backward pressure applied to the larynx to improve the view and in 431 patients without the pressure. In addition, 38 patients were measured after they had been reported "difficult to laryngoscope" by other anaesthetists.

Statistical analysis

Two groups of patients were formed—a "normal" group containing all 581 cases of grade 1–3 (with or without pressure) and a "difficult" group containing all 50 patients who were grade 4 or 5 despite attempts to improve the view by pressure on the larynx (the 12 patients in the initial series plus the 38 patients reported by colleagues). Features that might predict difficulty with intubation were examined individually for their ability to discriminate between normal and difficult groups. Clinical judgement and pairwise plotting of features were used to determine if particular combinations suggested high risk. A discriminant analysis of original and derived features (e.g. neck circumference/neck length) was carried out to find a predictive index based on a minimal number of measurements. Finally, an

TABLE II. *Continuous measurements compared between "normal" and "difficult" patients. P = Significance of two-sided two-sample* t *test*

	"Normal" (n = 581)			"Difficult" (n = 50)			
Feature	n	Mean	SD	n	Mean	SD	P
Age (yr)	365	44.8	19.8	19	46.3	14.0	0.74
Height (cm)	557	168.7	10.4	50	167.4	10.4	0.41
Weight (kg)	561	68.1	12.8	50	72.1	17.2	< 0.05
IG (cm)	580	4.6	1.0	50	3.8	0.7	< 0.05
ML (cm)	370	10.5	1.0	20	10.2	0.8	< 0.001
AM (cm)	120	3.4	0.7	20	3.7	0.4	0.15
PMD (cm)	370	3.1	0.5	20	2.9	0.4	0.06
NL (cm)	553	14.2	1.8	50	13.7	1.7	0.08
B (cm)	301	5.3	0.9	20	5.8	1.0	< 0.02
A+B (cm)	178	9.0	1.0	13	8.3	1.2	< 0.02
SLux (mm)	461	4.8	3.7	50	−0.5	4.7	< 0.001
NC (cm)	263	36.4	3.5	47	37.9	3.9	< 0.01
HFNF°	136	65.2	14.1	20	51.6	18.5	< 0.001
HENE°	136	61.9	17.0	20	42.1	19.9	< 0.001
HFNF°+HENE°	136	127.1	23.2	20	93.6	35.3	< 0.001
SC	124	58.1	15.0	16	54.5	13.2	0.36
L	89	−7.3	10.0	10	−11.2	13.4	0.27
NC/NL	263	2.5	0.4	47	2.8	0.4	< 0.001
Wt/NL	540	4.8	1.1	50	5.3	1.4	< 0.01
NC/Ht	262	0.55	0.05	47	0.57	0.06	< 0.02

TABLE III. *Final risk factors compared between "normal" and "difficult" patients. P = probability that difference between normal and difficult groups could arise by chance. For weight, the risk levels 0 and 1 were pooled and the difference tested by Fisher's Exact test; all other differences were tested with* χ^2

Risk factor	Risk level	Normal	Difficult	P
Weight	0	533 (95%)	45 (90%)	0.05
	1	27 (5%)	3 (6%)	
	2	1 (0.2%)	2 (4%)	
Head and neck movement	0	297 (91%)	27 (54%)	0.001
	1	21 (6%)	11 (22%)	
	2	8 (3%)	12 (24%)	
Jaw movement	0	457 (92%)	19 (38%)	0.001
	1	36 (7%)	17 (34%)	
	2	2 (0.4%)	14 (28%)	
Receding mandible	0	506 (97%)	29 (58%)	0.001
	1	16 (3%)	16 (32%)	
	2	1 (0.2%)	5 (10%)	
Buck teeth	0	504 (96%)	32 (64%)	0.001
	1	18 (3%)	12 (24%)	
	2	2 (0.4%)	6 (12%)	

extremely simple scoring system was investigated, and its predictive properties simulated.

Prospective trial

Eight anaesthetists (five consultants, one senior registrar and two registrars) agreed to use the scoring system and to assess the difficulty of laryngoscopy on a consecutive series of 778 patients for 2 months. Only one anaesthetist (M.W.) knew the rule that had previously been developed from the scoring system.

RESULTS

Initial study

Table I displays the number of patients who were classified in each grade of difficulty. The incidence of "difficult" laryngoscopy, that is, failure to see even the arytenoids, was 9.3%. However, if the larynx was pushed backwards to improve the view, the incidence of "difficulty" was 5.9%.

Summary statistics for features that might predict difficult laryngoscopy are shown in tables II and III. The data are presented, with the statistical significance of observed differences, for the two previously defined "normal" and "difficult" groups of patients. Many features were measured to see if they might be useful. In general, collection of a feature ceased when it was apparent that it had no value. The exact measurement of head and neck angles with a special apparatus was also discarded in favour of a simpler overall assessment.

TABLE IV. *The three levels of the final five risk factors. (* 5 cm is approximately three fingers' breadth)*

Risk factor	Level	
Weight	0	< 90 kg
	1	90–110 kg
	2	> 110 kg
Head and neck movement	0	Above 90°
	1	About 90° (ie. ± 10°)
	2	Below 90°
Jaw movement	0	IG ⩾ 5 cm* or SLux > 0
	1	IG < 5 cm and SLux = 0
	2	IG < 5 cm and SLux < 0
Receding mandible	0	Normal
	1	Moderate
	2	Severe
Buck teeth	0	Normal
	1	Moderate
	2	Severe

TABLE V. *Effect of varying the criterion for identifying "difficult" patients. True positive (%) = proportion of truly "difficult" patients correctly identified; false positive (%) = proportion of "not-difficult" patients wrongly identified as being at risk*

Risk sum criterion	True positive (%)		False positive (%)	
	Initial	Prospective	Initial	Prospective
⩾6		8	0	0
⩾5		17	0	0.3
⩾4	36	42	0	0.8
⩾3	52	50	1	4.6
⩾2	72	75	6	12.1
⩾1	86	92	24	26.2

Creating a predictive index

Linear discriminant analysis revealed that five risk factors, measured at three levels (table IV) provided significant discrimination; no others improved the prediction.

Two approaches to allocating a risk score to a new patient were investigated. The standard method is to add up the linear discriminant coefficients for the risk factors. The alternative, simpler method is to add up the observed risk levels (table IV), thus creating a "Risk-sum". Although one might expect the more complex discriminant analysis to perform better than the risk-sum method, it was found that the performance of the two methods was virtually indistinguishable when applied to the 344 patients in whom there was a complete set of measurements. The percentage of true positive and false positive predictions for each Risk-sum is shown in table V.

Prospective trial

Of the 778 patients studied, 12 (1.5%) were "difficult" (table I). Each patient was assessed using the simple scoring system and the percentage of true positive and false positive predictions for each Risk-sum are shown in table V.

DISCUSSION

In the initial study, when pressure was applied to the larynx, the incidence of difficult laryngoscopy was 5.9% (95% confidence limits 3.1–10.3%). In the prospective study involving a different group of anaesthetists the incidence was 1.5% (95% confidence limits 0.7–2.3%). This difference probably reflects either the eagerness of the investigators in the initial study to find examples of difficult intubation or a higher proportion of experienced anaesthetists in the second study. Nonetheless, even 1.5% is considerably greater than the 0.05% suggested by Cormack and Lehane [2] from their colleagues' "guestimates". The incidence of difficult *intubation* should be less than this because a tracheal tube may be passed through the cords even if they cannot be seen. On the other hand, sometimes the cords can be seen but there is difficulty passing the tube (e.g. because of an awkward peg tooth). Previous reports of the incidence of difficult intubation are quoted as 1%, 2.3% and 3.6% [1]. In obstetric anaethesia 2.7% of intubations are reported to be difficult (G. Lyons, personal communication) and the estimates for failed intubation are 0.05–0.3% [3, 4].

The linear discriminant analysis revealed that at least five factors contributed to difficult laryngoscopy, confirming clinical experience that no one factor can predict difficulty. Thus the adverse influence of one factor may be offset by other favourable features. For example, a patient may have severely limited movement of the head and neck and yet intubation may be easy because of great mobility of the lower jaw.

At intubation the neck needs to be flexed, with the head extended [5]; this is a complex manoeuvre and accurate measurement is difficult. X-ray evidence has indicated that limitation of the atlanto-occipital joint may be responsible for difficult intubation [6–9]. Although we have been unable to measure this clinically, we agree that some patients prove unexpectedly difficult to intubate because the head cannot be sufficiently extended on the neck.

Both SLux and IG are individually fairly powerful predictors of difficulty. However, the plot of IG against SLux showed a concentration of "difficult" patients in the bottom left hand corner which indicates an especial risk if both IG and SLux are low. Conversely, a low IG may not be dangerous if SLux is zero or greater; a finding in accord with clinical experience. Thus a predictive factor, "jaw movement", was created which depended on both IG and SLux (table IV).

Various derived ratios such as the neck circumference divided by neck length were designed to try and quantify "short fat neck" which is widely believed to be associated with difficult intubation. Although these derived ratios do predict difficult laryngoscopy (table II), none is simple to use; fortunately, weight itself was found to be satisfactory.

At laryngoscopy the line of sight extends from the laryngeal aperture to the tips of the upper incisors, which limit the view posteriorly. The view will be obstructed if, despite elevation with the laryngoscope blade, the tongue protrudes backwards across the line of sight. The expression "high anterior larynx" is sometimes offered as an explanation for a difficult intubation. Although it is not clear how the position is so judged, the implication is that the lower end of the line of sight is adversely shifted so that the tongue obstructs the view. We have tried many ways to estimate the position of the larynx relative to the tongue and other structures, but without much success. The measurement B, which estimates the length of the mandible behind the line of sight, is helpful but is associated with considerable inter-observer variation. Unusually long upper incisors (buck teeth) may adversely affect the position of the upper end of the line of sight and a receding mandible may indicate that the tongue is positioned more posteriorly than usual, blocking the view. Our analysis confirms the importance of both these factors and not surprisingly receding mandible, buck teeth, inter-incisor gap and subluxation were found to be correlated with one another (especially IG and SLux). Zuck [10] suggested that excessive anterior convexity of the cervical spine may be responsible for an "anteriorly situated larynx". Unfortunately, we have not found a suitable clinical measure.

Neither we (using external estimates of the posterior mandibular depth) nor others (using x-rays) [3, 9] have been able to confirm the predictive value of the posterior mandibular depth [6, 11].

A proposed index should be evaluated on a prospective data set, since the choice of features used in the creation of the index may be influenced by chance factors in the original data. Consequently, the predictive performance of an index might decrease when applied to new data. However, our index performed well on the prospective series of patients (table V). The true positive proportions were remarkably similar and the lower false positive proportions in the initial series may reflect the greater willingness of the authors, who carried out that study, to classify a patient as "difficult".

Although a test that picks up 75% of difficult laryngoscopies (using the Risk-sum criterion of $\geqslant 2$) appears valuable, the number of false alarms may be unacceptable. For example, if a Department anaesthetizes 10000 patients a year and the incidence of difficult laryngoscopy is 1.5%, then one might expect 150 difficult laryngoscopies and 9850 non-difficult laryngoscopies a year. With a false positive rate of 12.1%, 1191 patients a year would be falsely classified as at risk. In other words, skilled assistance would be called unnecessarily 99 times a month so that assistance could be at hand for nine of the 12 difficult laryngoscopies expected each month (the other three being missed); thus only 8% (9/9+99) of alarms would turn out to be necessary. Whether this is helpful or not will depend upon the geography and staffing arrangements of individual hospitals. Increasing the threshold to a criterion of $\geqslant 4$ would reduce the number of false alarms to seven per month at a cost of lowering the number of detected difficult laryngoscopies to five out of 12; thus 42% (5/5+7) of alarms would turn out to be positive.

Ideally, one might wish for a predictive test that picked up nine out of 10 difficult laryngoscopies at a cost of perhaps only one false alarm a week. However, because the incidence of difficult laryngoscopy is so low, this would require a test that was 90% specific and 99.5% sensitive—this is clearly unattainable! An important implication of this study is that, despite exploring many features, it was not possible to identify the difficult patients without the false positive rate increasing unacceptably. Inevitably, patients are at risk because the problem is unexpected. We conclude that it is essential that anaesthetists are aware of the inadequacy of attempts to predict difficult intubation and it is recommended that they practice simulated difficult intubations in the manner described by Cormack and Lehane [2]. Finally, they should be able to fall back upon a clear "difficult intubation drill" or, if necessary, a simple cricothyroidotomy procedure.

ACKNOWLEDGEMENTS

We are grateful to our colleagues at the Royal United Hospital, Bath and the Royal Naval Hospital Plymouth for their enthusiastic support and assistance in collecting data.

REFERENCES

1. Latto IP, Rosen M. *Difficulties in Tracheal Intubation.* Eastbourne: Baillière Tindall, 1985.
2. Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. *Anaesthesia* 1984; **39**: 1105–1111.
3. Lyons G. Failed intubation. Six years' experience in a teaching maternity unit. *Anaesthesia* 1985; **40**: 759–762.
4. Lyons G, MacDonald R. Difficult intubation in obstetrics. *Anaesthesia* 1985; **40**: 1016.
5. Bannister FB, Macbeth RG. Direct laryngoscopy and tracheal intubation. *Lancet* 1944; **2**: 651–654.
6. White A, Kander PL. Anatomical factors in difficult direct laryngoscopy. *British Journal of Anaesthesia* 1975, **47**: 468–474.
7. Nichol HC, Zuck D. Difficult laryngoscopy—the 'anterior' larynx and the atlanto-occipital gap. *British Journal of Anaesthesia* 1983; **55**: 141–144.
8. Skues M. Anatomical factors complicating direct laryngoscopy. *Anaesthesia Points West* 1984; **18**: 31–33.
9. Levack ID, Masson AHB. Difficult tracheal intubation. *Anaesthesia* 1986; **41**: 332.
10. Zuck D. Difficult tracheal intubation. *Anaesthesia* 1985; **40**: 1016–1017.
11. Evans R, Cormack RS. Difficult intubation. *Anaesthesia Points West* 1984; **17**: 79–80.

Note added in proof. Since the manuscript was accepted for publication Samsoon and Young (*Anaesthesia* 1987; **42**: 487–490) have advocated the Malampatti test (*Canadian Anaesthestists' Society Journal* 1985; **32**: 429–434). They examined 13 patients known to be difficult subjects for intubation and, with the exception of one patient with tracheal stenosis, found that in every patient the uvula and soft palate were obscured by the tongue. Unfortunately, they did not report the incidence of this sign in patients who were not difficult to intubate. However, it is possible to evaluate the performance of the test from data presented in table II of the Malampatti paper. If Class 3 (only soft palate could be visualized) is used as the criterion to predict difficult laryngoscopy, then it can be calculated that the false positive rate was 5% for a true positive rate of only 55%.

Br. J. Anaesth. (1988), **61**, 217–220

LEARNING FIBREOPTIC INTUBATION: USE OF SIMULATORS *V*. TRADITIONAL TEACHING

A. OVASSAPIAN, S. J. YELICH, M. H. M. DYKES AND M. E. GOLMAN

SUMMARY

This study compared a graduated training programme with that of a traditional teaching method to facilitate the learning of the technique of fibreoptic nasotracheal intubation. Thirty-two anaesthesia trainees were randomly assigned to two groups. The graduated programme involved: practice on a bronchoscopy teaching model; exposure of the epiglottis and vocal cords in patients recovering from general anaesthesia; performance of fibreoptic nasotracheal intubation in awake sedated patients. The traditional programme involved: demonstration (on a patient) of one fibreoptic nasotracheal intubation by the instructor; performance of fibreoptic nasotracheal intubation (by the trainee) in awake sedated patients. Nasotracheal intubation was accomplished significantly more often by the trainess in the graduated programme (86 out of 96 (89.6%) v. 64 out of 96 (66.5%) ($P < 0.01$). The results demonstrate that trainees who undergo a graduated training programme using simulators are initially more successful at awake fibreoptic nasotracheal intubation than those who have learned in the traditional manner, and that the conditions of the investigation were acceptable to the trainees and patients.

A graduated training programme developed to facilitate learning of nasotracheal intubation using flexible fibreoptic endoscopes has been described in detail [1]. The programme was developed to provide a means of overcoming the apparent reluctance of established clinicians, and trainees, to attempt a new technique associated with a high incidence of failure. It was based on current educational principles for teaching and learning a psychomotor skill [2–4], and included graduated learning objectives, and both model and live patient simulators.

Several factors suggested that the programme was highly successful: the high success rate (74 successful intubations out of the 75 attempted); the short average time for intubation upon completion of the programme (average 3.3 min); the high incidence of patient satisfaction; and the highly positive regard in which the trainees held the programme. Although a number of reports of the use of various types of models as simulators have appeared in the medical education literature over the past 15 years [5–15], few have included the use of control groups and randomized assignment of trainees [5,7,11] to document their true value. Although these three studies documented the value of the simulators, in one [5] the simulator was a sophisticated computer-controlled anthropometric manikin, while in another [11] the learners demonstrated their improved performance on the simulator itself, not on patients in the "real world" of clinical practice.

This study was undertaken to evaluate this graduated training programme, by assessing the effectiveness of learning on simulators before an unassisted fibreoptic intubation was attempted in the operating theatre. It compared the success of the initial attempts to perform fibreoptic intubation in patients in the operating theatre between two groups of randomly selected anaesthesia trainees. It seems reasonable to conclude that a learner's initial attempts at a new technique are the most hazardous for the patients and the most stressful, not only for the learners and their teachers, but also for established clinicians who

---

ANDRANIK OVASSAPIAN, M.D.; SHARON J. YELICH, M.D.; MICHAEL H.M. DYKES, M.D., M.ED.; Anesthesia Department, Northwestern University School of Medicine, and Anesthesia Service Veterans Administration Lakeside Medical Center, 333 East Huron Street, Chicago, Illinois 60611, U.S.A. (The late) MELTON E. GOLMAN, PH.D., Office of Medical Education, Northwestern University School of Medicine, 333 East Chicago Avenue, Chicago, Illinois 60611, U.S.A. Accepted for Publication: January 9, 1988.

Correspondence to A. O.

are teaching themselves. The study group underwent the graduated programme, while the control group learned from a traditional "see one, do one" teaching method.

MATERIALS AND METHODS

Twenty-eight anaesthesia residents and four oral surgery residents rotating through the Anesthesia Service participated in the study. They were randomly assigned by use of a random number table either to the experimental group which entered the graduated training programme or to the control group which received traditional teaching on patients in the operating theatre.

(A) The graduated training programme consisted of three phases after demonstration of the fibreoptic laryngoscope (Machida America Inc. Model FLS-6-50) by the instructor, and has been described in detail previously [1]: (1) Model simulator; practice on bronchoscopy teaching model. (2) Live patient simulator; exposure of epiglottis and vocal cords in patients who had given informed consent and who were recovering from general anaesthesia in the recovery room. (3) Fibreoptic nasotracheal intubation in six awake sedated patients in whom such intubation was indicated. The time from the introduction of the fibrescope into the tracheal tube to completion of intubation was recorded with a stop watch. If the trainee failed to expose the vocal cords within 4 min, the intubation was considered failed, and verbal comments and directions were given. If the vocal cords were not located within the next 2–3 min the instructor exposed them and the trainee completed the intubation.

(B) The traditional teaching method consisted of two phases after demonstration of the fibreoptic laryngoscope by the instructor: (1) Demonstration of one fibreoptic nasotracheal intubation. After assisting with the sedation and performance of topical anaesthesia, the instructor described the technique in detail and demonstrated the anatomical landmarks through the fibrescope while performing the endoscopy. (2) Fibreoptic nasotracheal intubation in six awake sedated patients in whom such intubation was indicated.

In order to compare the rate of successful intubation in the two groups, each trainee was assigned a single score equal to the number of successful intubations s/he performed out of the six attempts at intubation. The scores for all the trainees were then treated as ordinal data and the two groups were compared using the Mann–Whitney *U* test. The null hypothesis that there was no difference between the two groups was to be rejected if $P < 0.05$. Two additional supporting numerical comparisons, between the performance of the two groups on their first six attempts at intubation, were used, without additional statistical tests to avoid the beta-type error inherent in the use of multiple such tests on the same data: (1) Percentage of trainees successful in all intubation attempts. (2) Percentage of instances in which the instructor had to expose the vocal cords. All trainees were interviewed on completion of their training, and postoperative visits were conducted on all patients in whom the trachea had been intubated.

RESULTS

The age distribution, American Society of Anesthesiologists' physical status classification, indication for fibreoptic nasotracheal intubation and type of operation, were similar in the two groups of patients. The duration of anaesthesia training before attempting the first fibreoptic intubation in the experimental group averaged 7.4 months (range 2–22 months), compared with 8.5 months (range 1.5–20.5 months) in the control group. There were 11 male and five female trainees in the experimental group, and 10 male and six female trainees in the control group. The number of dentists in each group was three and one, respectively.

The experimental group took an average of 6.5 h to complete this programme: 1 h for the demonstration by the instructor of both the equipment and use of the model; an estimated 2 h for practising on the model without the instructor; 1.5 h for six laryngeal exposures; 2 h for six actual intubations. The control group took an average of 3.5 h: 1 h for a demonstration of equipment; 0.5 h for the demonstration of one

TABLE I. *Number of trainees who achieved varying numbers of successful intubations.* **P < 0.01 *using Mann–Whitney* U *test comparing all successful intubations in experimental group* v. *control group*

	No. of successful intubations						
	0	1	2	3	4	5	6
Experimental** ($n = 16$)	0	0	0	1	1	5	9
Control ($n = 16$)	1	0	1	3	5	3	3

intubation; 2 h for six actual intubations. The time spent by the instructor in teaching averaged 4.5 h for each trainee in the experimental group and 3.5 h for each trainee in the control group. The major difference between the groups was the 3.5 h spent by each trainee in the experimental group in practising psychomotor skills on simulators before attempting an intubation in a patient in the operating theatre. In place of this the control group watched a demonstration lasting 0.5 h before attempting an intubation in a patient. This is the method traditionally used by anaesthetists when teaching psychomotor skills.

The trainees in the experimental group were successful in 86 out of the 96 (89.6 %) intubation attempts; the trainees in the control group were successful in 64 out of the 96 (66.5 %) intubation attempts. A comparison of the number of successful intubations performed by each trainee is displayed in table I. The Mann–Whitney *U* test gave a value of $P < 0.01$, and resulted in rejection of the null hypothesis. This was supported by both of the additional numerical comparisons. In the experimental group nine of 16 (56.2 %) trainees were successful in all six actual intubations, while in the control group three of 16 (18.8 %) trainees were successful in all six intubations. In only one out of 96 intubation attempts (1 %) in the experimental group did the instructor have to identify the cords. In the control group the instructor had to identify the vocal cords on 14 occasions (14.6 %).

The interviews with the trainees in the experimental group indicated that, subjectively, they felt that the training on the model, and on patients recovering from general anaesthesia, had been helpful. Four indicated that the time spent on the model and in the recovery room could be reduced; only two indicated a need to perform more intubations, and one felt the pressure of being timed in the operating room. Their comments on the weaknesses of the programme were focused primarily on the need to obtain informed consent. Five trainees in the control group indicated that they were "not comfortable" using the fibrescope. Three felt the pressure of being timed in the operating room, three indicated that they would have liked to have worked on the model and to have experience on patients in the recovery room, and three indicated that they would have benefited from more experience of intubation. The postoperative visits (after all 192 intubation attempts) revealed that 75 (39 %) patients had recall, but that although seven found the procedure unpleasant because of pain during the passage of the tube through the nares, only three would prefer not to undergo it again. These few complaints were voiced by the patients of both group of trainees.

DISCUSSION

As none of the trainees in the experimental group had had previous exposure to fibreoptic intubation, compared with two trainees in the control group who, after completion of their training, indicated that they had limited experience with flexible fibreoptic bronchoscopes, the better performance of the experimental group on their initial attempts to perform fibreoptic intubation on patients in the operating theatre can be attributed to the graduated training programme, and the 3.5 h spent learning and practising psychomotor skills on the simulators. Support for, but not additional proof of these data, stems from two observations. First, the instructors' routine observations suggested that trainees in the experimental group demonstrated more confidence and were more skilful in handling the fibrescope. Second, clear communication between the instructor and the experimental group of trainees was easily established while with the control group it was difficult to establish because of the latter group's lack of familiarity with the instrument and of the actual technique of fibreoptic intubation. Trainees in the control group often had to be reminded of the steps, and shown how to hold the instrument and use the control knob.

The advantages of this graduated training programme appear to be: every anaesthetist can follow the steps and so train himself or herself in the use of these instruments; the ability to hold and manipulate the fibrescope and to appreciate the view through it can be learned with unlimited time on an artificial model; exposure of the vocal cords in patients recovering from general anaesthesia provides a convenient and non-stressful environment for gaining experience in the use of the fibrescope in humans, for identification of laryngeal structures, and for recognizing the problems created by secretions; the experience gained by exposing the larynx in the recovery room also generates the confidence in the trainee which is a critical factor for success in the first patient for whom it is used in the operating theatre; having learned the basics of the psychomotor skill on simulators, the learner can concentrate on perfecting his/her technique in patients, and thereby make more efficient use of the limited number of such patients who are available; the prior experience gained from the simulators should minimize the time taken to acquire an adequate level of skill, and decrease the risk inherent in learning from scratch on patients in the "real world" of clinical practice; the reactions of both the residents and the patients indicate a high degree of acceptability.

The disadvantages of this graduated training programme appear to be the additional 3 h of work undertaken by the trainees before they attempted to intubate a patient in the theatre environment; the additional 1 h spent by the instructor in teaching the trainees; the need to obtain the informed consent of the patients who would act as "simulators" while recovering from general anaesthesia.

Clearly, it is as difficult for an established clinician with no previous training in fibreoptic endoscopy to introduce the technique into his/her practice as it is for an anaesthesia trainee to learn the skill. It is also clear that, even if an expert instructor is available (as in training programmes), there are numerical limitations to providing extensive training by utilizing only patients in the operating theatre. We believe this study documents the effectiveness of learning on simulators before an unassisted fibreoptic intubation is attempted in the operating theatre and, therefore, provides a solution to both of the above educational problems.

In summary, this programme affords the learner, including the established clinician attempting to teach him/herself, ample opportunity to practise the various parts of the skill in increasingly more complex circumstances by utilizing simulators. It culminates in a high rate of success when the learners first attempt to perform unassisted fibreoptic intubations in patients in the operating theatre. In addition, the limited number of patients available who require such a technique can be utilized more efficiently.

ACKNOWLEDGEMENT

The authors acknowledge with thanks the assistance of Michael J. Avram, PH.D. in statistical analysis on the data, and of Ms Patricia A. Hundon for typing the manuscript.

REFERENCES

1. Ovassapian A, Dykes MHM, Golman ME. A training programme for fibreoptic nasotracheal intubation. Use of model and live patients. *Anaesthesia* 1983; 38: 795–798.
2. Davis RH, Alexander LT, Yelon SL. The learning and teaching of preceptualmotor skills. In: *Learning System Design: An Approach to the Improvement of Instruction.* New York: McGrawHill, 1974; 279–299.
3. Foley RP, Smilansky J. Skill lessons. In: *Teaching Techniques: A Handbook for Health Professionals.* New York: McGraw-Hill, 1980; 71–91.
4. Menges RJ. Instructional methods. In: Chickering AW, ed. *The Modern American College.* San Francisco: Jossey-Bass, 1981; 556–581.
5. Abrahamson S, Denson JS, Wolf RM. Effectiveness of a simulator in training anesthesiology residents. *Journal of Medical Education* 1969; 44: 515–519.
6. Calderwood HW, Ravin MB. The cat as a teaching model for endotracheal intubation. *Anesthesia and Analgesia* 1972; 51: 258–259.
7. Penta FB, Kofman S. The effectiveness of simulation devices in teaching selected skills of physical diagnosis. *Journal of Medical Education* 1973; 48: 442–445.
8. Howells TH, Emery FM, Twentyman JEC. Endotracheal intubation training using a simulator. An evaluation of the Laerdal adult intubation model in the teaching of endotracheal intubation. *British Journal of Anaesthesia* 1973; 45: 400–402.
9. Sackner MA. Bronchofiberscopy. *American Review of Respiratory Disease* 1975; 111: 62–88.
10. Kisling JA, Schreiner RL. The kitten as a teaching model for intubation of the human neonate. *Respiratory Care* 1976; 21: 1243–1246.
11. Sajid A, Magero J, Feinzimer M. Learning effectiveness of the heart sound simulator. *Medical Education* 1977; 11: 25–27.
12. Schreiner RL, Gresham EL, Escobedo MB, Gosling CG. Umbilical vessel catheterization. A teaching simulator. *Clinical Pediatrics* 1978; 17: 506–508.
13. Gordon MS, Ewy GA, DeLeon AC, Waugh RA, Felner JM, Forker AD, Gressner IH, Mayer JW, Patterson D. "Harvey" the cardiology patient simulator: Pilot studies on teaching effectiveness. *American Journal of Cardiology* 1980; 45: 791–796.
14. Guenther SM, Laube DW, Matthes S. Effectiveness of the gynecology teaching associate in teaching pelvic examination skills. *Journal of Medical Education* 1983; 58: 67–69.
15. Sankaran K, Yadlapalli J, Zakhary GX. Evaluation of a teaching method for endotracheal intubation in neonates. *Annals of Royal College of Physicians and Surgeons of Canada* 1985; 18: 135–136.

Br. J. Anaesth. (1988), **61**, 221–227

THE MORPHINE HYDROGEL SUPPOSITORY

A New Sustained Release Rectal Preparation

C.D. HANNING, A.P. VICKERS, G. SMITH, N.B. GRAHAM
AND M.E. McNEIL

SUMMARY

The morphine hydrogel suppository (MHS), a monolithic sustained release rectal preparation, has been developed and evaluated in three pilot studies. Two release profiles have been prepared. The first, MHS(B), has a high initial release rate followed by a constant release for the remainder of a 12-h period. The second, MHS(S), has the same constant release rate for 12 h. MHS(B) is intended to attain and maintain analgesic or near analgesic plasma concentrations of morphine, and MHS(S) to maintain that concentration for successive 12-h periods. The pilot studies suggest that MHS may be of value in the management of postoperative pain.

The most widely practised technique for the relief of postoperative pain is the i.m. injection of an opioid administered on an intermittent "on-demand" basis. It is generally accepted that the failure to anticipate pain and the variations in the plasma drug concentration associated with this technique result in poor analgesia and frequent side-effects, and that the continuous administration of an appropriate drug is preferable.

The rectal route of administration is suitable for sustained release preparations [1], but is not often considered by British physicians [2]. A new, monolithic sustained-release morphine hydrogel suppository (MHS), capable of attaining and maintaining analgesic or near-analgesic blood concentrations of morphine has been developed, and then evaluated in three pilot studies in patients with postoperative pain.

DEVELOPMENT OF THE MORPHINE HYDROGEL SUPPOSITORY

Hydrogels

Hydrogels are crystalline-rubbery compounds based on cross-linked ethylene oxide [3]. They are insoluble in water, biologically inert and hydrophilic. In the dehydrated form they are firm and can be moulded and shaped. When hydrated they swell to two to four times the original volume and become soft and rubbery. They can be impregnated with water- or alcohol-soluble drugs which are released on rehydration in a reproducible and predictable manner. The rate of release is determined by the chemical composition of the hydrogel and its rate of rehydration, the surface area and thickness of the block of hydrogel and the concentration of drug within the matrix. Early studies using prostaglandin E_2 confirmed that predictable release profiles could be obtained, and that particular preparation has been used to facilitate cervical ripening in labour [4]. An additional benefit was the improved temperature stability of the prostaglandin in the hydrogel matrix.

Pharmacokinetic theory suggests that the attainment of a steady blood concentration of a drug with a constant infusion requires a time equal to four to five times the elimination half-life ($T_{\frac{1}{2}}^{\beta}$) of the drug. The $T_{\frac{1}{2}}^{\beta}$ for morphine is 2–3 h and, consequently, an initial bolus of morphine is required in order to accelerate the attainment of a steady-state concentration. Thus the ideal release profile should incorporate both a bolus and a continuous release of morphine in order to ensure a rapid onset of action.

C.D. HANNING, B.SC., F.F.A.R.C.S.; A.P. VICKERS*, F.F.A.R.C.S.; G. SMITH, M.D., F.F.A.R.C.S; University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW. N.B. GRAHAM, PH.D., F.R.S.C.; M.E. McNEIL; Department of Pure and Applied Chemistry, University of Strathclyde, Glasgow G1 1XL. Accepted for Publication: February 9, 1988.

*Present address: Department of Anaesthesia, Royal Lancaster Infirmary, Lancaster LA1 4RP.

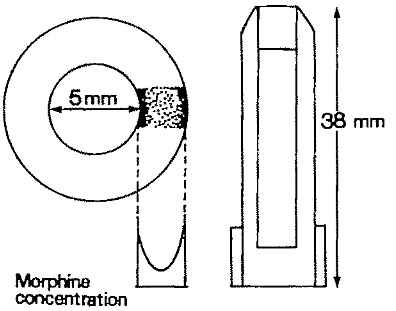


FIG. 1. A prototype morphine hydrogel suppository. The concentration of morphine within the matrix is highest at the outer and inner surface.

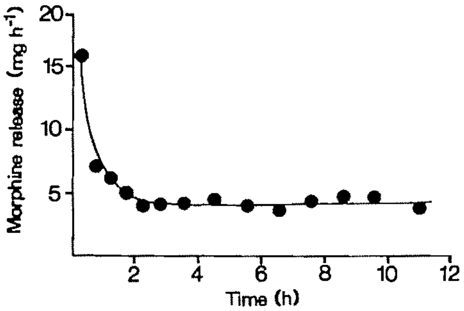


FIG. 2. *In vitro* release profile of a protoype morphine hydrogel suppository at 37 °C.

Prototype MHS (I)

A number of hydrogel configurations were tested *in vitro* for a suitable release profile [5]. The most suitable was a hollow cylinder with closed ends (fig. 1). The concentration of morphine was arranged to be greatest at the outer and inner surfaces, giving the release profile closest to that thought to be ideal (fig. 2). The choice of bolus and constant-release dose was complicated by the paucity of information on the rectal bioavailability of morphine. An estimated dose of a 10-mg bolus and a constant release of 4 mg h^{-1}, to err on the side of safety, was chosen. The bolus and release rate achieved *in vitro* were 11.4 mg and 4.1 mg h^{-1}. A silicone rubber collar was fitted to the base of the suppository to anchor a thread which could enable the device to be withdrawn in the event of overdose. This and subsequent developments were evaluated in the series of pilot studies outlined below. The initial study showed that a greater dose was required and that some flexibility in dosage would be advantageous.

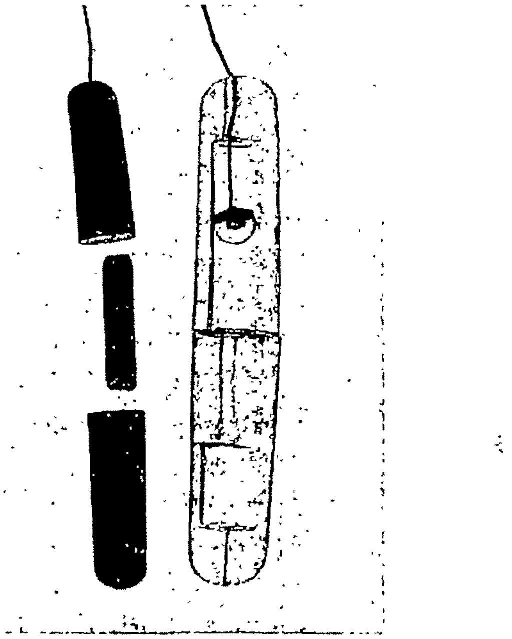


FIG. 3. Second prototype morphine hydrogel suppository shown in the hydrated (right) and dehydrated (left) states. The method of joining the two half suppositories with a rod of hydrogel is also shown.

Prototype MHS (II)

The total dose and rate of release of morphine were increased by equilibrating the hydrogel at 37 °C. (The solubility of morphine increases with temperature, allowing a higher concentration to be achieved.) The overall size of the suppository was increased and the shape changed to a smoother outline. Two half suppositories (fig. 3) were joined by a short length of hydrogel rod. One half was drilled through the closed end to take a withdrawal thread. Two different strengths of half suppository were prepared, giving boluses of 6 mg and 10 mg and infusion rates of 2.5 and 3.6 mg h^{-1}, respectively. Three different strengths of suppository were thus available by joining two halves with a rod of hydrogel, giving single doses of 12, 16 and 20 mg, infusion rates of 5, 6.1 and 7.2 mg h^{-1} and total contents of 76, 103 and 130 mg morphine, respectively.

Prototype MHS (II)

The need to continue the administration of morphine beyond the first 12 h necessitated the development of an MHS with a different release profile since repeated administration of the bolus and sustained release suppository (MHS(B)) could result in overdose during the hours immediately following the second and subsequent insertions. A sustained-release only (MHS(S)) suppository was developed so as to permit administration for successive 12-h periods after the administration of an MHS(B).

Two strengths of suppository were prepared. The "high" dose MHS(B) contained morphine 130 mg released as a 16-mg single dose, followed by a constant release of 6.9 mg h^{-1} and the matching MHS(S) had a similar constant release rate and contained morphine 120 mg. The "low" dose (MHS(B)) contained morphine 105 mg with single dose and constant release of 10 mg and 5.5 mg h^{-1}, respectively. The low dose MHS(S) contained morphine 100 mg at the appropriate release rate.

EVALUATION OF PROTOTYPE MHS

Patients and Methods

The prototype MHS were evaluated in a series of pilot studies. The studies were approved by the District Ethical Committee and all patients gave their informed consent.

Pilot study I

Prototype MHS(I) were administered to four healthy patients (two male) of mean age 39.5 yr (range 22–54) and mean weight 79 kg (67–89)[6].

The suppositories were administered 2–12 h before surgery and further analgesia provided with pethidine i.m. on demand. Venous blood samples were drawn before insertion and 30, 60, 90, 120, 180 and 240 min thereafter and, subsequently, at least every 240 min up to 720 min. Plasma morphine concentrations were determined by high pressure liquid chromatography (HPLC)(7).

The suppositories were readily and painlessly inserted and removed and the patients were unaware of them whilst *in situ*. The plasma morphine concentrations attained are shown in figure 4. There was considerable variation between the subjects, although there was a general impression of the attainment of a plateau 2 h after administration which was maintained for the subsequent 10 h.

A further patient underwent excision of the rectum for carcinoma 12 h after the administration of an MHS(I). Histological examination of the mucosa adjacent to the suppository showed no abnormality.

The concentrations of morphine attained were less than those usually associated with adequate analgesia.

Pilot study II

Twelve otherwise healthy patients (five male) about to undergo a surgical procedure normally requiring postoperative opioid analgesia were studied (8). An MHS (II) selected according to the patient's weight and proposed operation was administered 2 h before surgery. Patients weighing less than 50 kg received the lowest strength, those from 50 to 70 kg the median strength and those more than 70 kg the highest strength. Anaesthesia was induced and maintained by conventional techniques, further intraoperative analgesia being provided with fentanyl at the anaesthetist's discretion. Additional postoperative analgesia was given as pethidine at the discretion of the nursing staff.

Venous blood samples were drawn before insertion of the MHS(II) and then 30, 60, 90, 120,

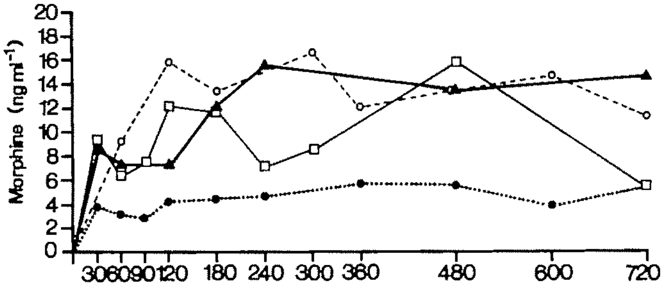


FIG. 4. Plasma morphine concentrations with time in four patients following the administration of a prototype MHS(I).

240, 360, 480 and 720 min thereafter, and plasma morphine concentrations were measured by HPLC. Technical difficulties with the assay resulted in plasma morphine concentrations being available for only nine subjects.

The demographic data, operation and dose of morphine administered are shown in table I. The suppositories were easily and painlessly inserted. The fully hydrated suppository was undetectable *in situ* by the patient. Plasma morphine concentrations (table II) were slightly greater than with the first prototype and showed a similar time course. No formal estimations of analgesia or nausea were undertaken, but it was noted that only three patients required additional intra- and postoperative opioid drugs. All three were undergoing upper abdominal surgery. Only one patient, who underwent cholecystectomy, complained of nausea of severity sufficient to merit the administration of an antiemetic drug.

Pilot study III

The third pilot study was designed to examine the changes in plasma morphine concentration during the period following the change from an MHS(B) to an MHS(S)[9]. Linear analogue scores (LAS) for pain, nausea, sedation and dizziness were also recorded. A similar group of patients receiving conventional analgesia (intermittent i.m. injection of morphine) were similarly studied in an open design to provide some basis for comparison.

Eighteen healthy women undergoing abdominal hysterectomy were allocated randomly to receive analgesia by either MHS or i.m. morphine for the first 24 h after surgery. Those receiving MHS and weighing more than 70 kg were given the "high" dose; the "low" dose was given to those patients who weighed less than 70 kg.

The MHS(B) was administered 2 h before operation and the MHS(S) 12 h later. Further analgesia was provided with i.m. pethidine 75–100 mg as required. The i.m. morphine group received morphine 10 mg 1 h before surgery and the same dose on demand in the postoperative period. Both groups also received an antiemetic before and after the surgical procedure, as required. The anaesthetic technique was standardized, fentanyl being given as required.

Venous blood samples were drawn and LAS

TABLE I. *Demographic data, operation and total morphine dose in patients given an MHS(II). F = Intraoperative fentanyl; P = postoperative pethidine; N = nauseated*

Patient No.	Operation	Sex	Age (yr)	Wt (kg)	Morphine dose (mg)
1	Tubal ligation	F	45	66	103
2	Gastrectomy	M	65	75	130(FP)
3	Varicose vein stripping	F	48	105	130
4	Scaphoid graft	M	34	85	130
5	Tubal ligation	F	40	47	76
6	Spinal fusion	M	78	76	130
7	Coracoid transfer	M	24	80	130
8	Vagotomy and pyloroplasty	F	53	66	103(FP)
9	Excision of rhinophyma	M	63	84	103
10	Cholecystectomy	F	35	70	103(FPN)
11	Extraction of molar teeth	M	25	85	103
12	Mastectomy	F	68	71	103

TABLE II. *Plasma morphine concentrations (ng ml^{-1}) following the administration of an MHS(II) in nine patients*

	Time (min)							
	30	60	90	120	240	360	480	720
Mean	3.0	5.3	7.8	8.9	15.3	16.5	17.3	16.9
SEM	1.0	1.3	1.7	1.7	2.3	2.5	2.4	1.5
Range	0–7.5	0–11.0	0–13.7	1.2–16.8	5.0–25.5	6.7–30.5	9.7–31.8	13.3–26.2

completed at 4, 12, 13, 14 and 24 h after the commencement of the study in both groups. No attempt was made to co-ordinate i.m. injections and sample times. Patients were also asked to complete an LAS for their average and maximum pain at the end of the study period.

Eight patients received MHS and 10 received i.m. morphine. One patient given MHS was withdrawn from the study following a hypotensive episode after a dose of pethidine: the MHS was removed and a full recovery ensued with i.v. fluid replacement. Two patients given i.m. morphine were withdrawn: one because a hysterectomy was not performed and the other for a presumed reaction to morphine.

There was no significant differences between the groups with regard to age or weight.

The plasma concentrations of morphine are shown in figure 5. The plasma concentrations of morphine were maintained during the change from MHS(B) to MHS(S) without any consistent pattern of an increase or diminution. The concentrations achieved with MHS were less than those achieved with i.m. morphine, although with less scatter, as would be expected.

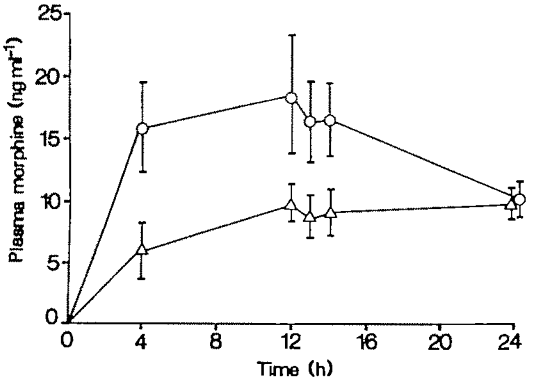


FIG. 5. Mean (SEM) plasma morphine concentrations with time in seven patients following the administration of an MHS(B) at 0 h and an MHS(S) at 12 h (△) and in eight patients given i.m. morphine on demand (□).

The mean LAS for pain were less in the MHS group than the i.m. morphine group (table III). The LAS for maximum pain was significantly less for the MHS group than for the i.m. morphine groups ($P < 0.05$) (Rank Sum Test).

The MHS group received a mean of 4.2 doses of pethidine (range 1–5) and the i.m. group a mean of 4.5 doses of morphine (range 3–6).

The mean LAS for nausea were also less in the MHS group. The MHS group required significantly fewer doses of antiemetic (mean 2.4 range 0–7) than the i.m. morphine group (mean 5.4 range 4–7) ($P < 0.01$, Student's t test).

There were no significant differences between the groups with respect to sedation or dizziness. All the patients receiving MHS preferred them to injections. One patient who received i.m. morphine preferred injections, another preferred suppositories, and the remainder had no opinion.

DISCUSSION

The constant administration of an opioid to provide steady plasma concentrations of the drug should provide better analgesia than intermittent administration in the management of postoperative pain, since the peaks and troughs of plasma concentrations are avoided. The rectum is a suitable site for the administration of drugs, particularly from sustained-release preparations [1]. There is a partial bypassing of first-pass hepatic metabolism, the degree being determined by the anatomical arrangement of the venous drainage in an individual and the position in the rectum of the preparation. Considerable differences in rectal/parenteral availability occur between different individuals, but there is little variation with time within one individual. The rectal/parenteral availability for morphine would appear to be between 0.3 and 0.15; that is, the rectal dose should be three to six times higher than the parenteral dose to achieve similar plasma concentrations [10]. The rate of absorption

TABLE III. *Mean (SEM) linear analogue scores (cm) for pain following administration of an MHS(B) and an MHS(S)* (n = 7) *and with the intermittent administration of i.m. morphine on demand* (n = 8). *Average and maximum pain scores were taken at 24 h.* *P < 0.05

	Time after administration (h)					
	4	8	12	24	Average	Maximum
MHS ($n = 7$)	2.4 (0.69)	3.5 (0.89)	3.1 (0.98)	1.9 (0.95)	4.1 (0.59)	5.9 (0.47)
I.m. morphine ($n = 8$)	3.9 (1.4)	5.2 (0.8)	3.6 (1.0)	3.5 (1.1)	5.0 (0.86)	8.4 (0.54)*

through the rectum is slow compared with i.m. injection and is dependent on the formulation [11]. Rectal administration is thus unsuitable for the management of acute pain, unless it can be foreseen—as with operative and postoperative pain—and is more suited to the management of chronic pain. The ability to remove a suppository readily in the case of an adverse reaction or overdose is an additional margin of safety over oral administration.

The hydrophilic polymer gels (hydrogels) have a number of features which make them suitable vehicles for sustained administration of drugs. They are biologically inert and rehydration and drug release are predictable and reproducible. The variation of drug concentration within the polymer matrix permits differing release profiles. In this case, the ability to release a "bolus" dose followed by a constant release rate is essential for a drug such as morphine with a $T_{\frac{1}{2}}^{\beta}$ of long duration. The monolithic nature of the hydrogel suppositories precludes a sudden release of the contained drug unless the device is divided into many small pieces, thus increasing the surface area. The dehydrated suppositories may be cut with a knife, thus offering the potential of varying the dose to suit individual patients.

These three pilot studies, on progressive developments of the prototype MHS, confirm that the release profile provided is able to maintain analgesic or near analgesic plasma concentrations of morphine for up to 24 h. The attainment of the plateau concentration requires 2–4 h after insertion, thus making the devices unsuitable for the management of acute pain if given alone. The variations between individuals in pain perception, sensitivity to analgesics and rectal absorption make it highly unlikely that one or two strengths of suppository will be able to provide adequate analgesia for more than a few subjects. This is particularly so if the dose errs on the side of safety.

Pain is not necessarily constant throughout the postoperative period and an increase in pain may follow movement, visceral spasm or procedures such as physiotherapy. Constant release devices such as the MHS which provide a "background" concentration of analgesic at an analgesic or sub-analgesic level will also require the addition of small supplementary doses of analgesic to counter these transient increases in pain. The patient may not be spared any injections, but the reduced variation in plasma concentrations may improve overall analgesia and reduce side-effects such as nausea. The pilot studies reported here to tend to confirm this hypothesis, although the number of patients studied and the trial designs preclude confirmation.

Hydrogels are potentially useful vehicles for the programmed sustained release of many drugs. MHS would appear to be a useful addition to our analgesic armamentarium. The preliminary studies suggest that a formal clinical trial is justified. Evaluation of MHS in the management of chronic pain is also appropriate.

ACKNOWLEDGEMENTS

We thank Sister P. Parry for her practical help, the anaesthetists, surgeons and ward staff of the Leicester General Hospital and Leicester Royal Infirmary for their forebearance, Mr K.J. Achola for the morphine assays and the Pharmacy, Leicester General Hospital, for their assistance. We gratefully acknowledge the financial support of Trent Regional Health Authority, the National Research and Development Corporation, the Science and Education Research Council and the Association of Anaesthetists.

REFERENCES

1. de Boer AG, Moolenaar F, de Leede LGJ, Breimer DD. Rectal drug administration: clinical pharmacokinetic considerations. *Clinical Pharmacokinetics* 1982; 7: 285–311.
2. Anonymous. Suppositories for systemic medication: an underused approach. *Drug and Therapeutics Bulletin* 1983; 21: 53–54.
3. Graham NB, Nwachuku NE, Walsh DJ. Interaction of poly (ethylene oxide) with solvents: 1. Preparation and swelling of a cross-linked poly (ethylene oxide) hydrogel. *Polymer* 1982; 23: 1345–1349.
4. Graham NB, McNeill ME, Zulfiqar M, Embrey MP. Hydrogels for the controlled release of prostaglandin E_2. *ACS Polymer Reprints* 1980; 21: 104–107.
5. McNeill ME, Graham NB. Morphine hydrogel suppositories: Device design, scale-up and evaluation. In: Ping ILE, Good WR, eds. *Controlled Release Technology; Pharmacology Applications*. American Chemical Society Symposium Series 348, 1987; 158–170.
6. Hanning CD, Smith G, McNeill M, Graham NB. Rectal administration of morphine from a sustained release hydrogel suppository. *British Journal of Anaesthesia* 1983; 55: 236P.
7. Aitkenhead AR, Vater M, Achola K, Cooper CMS, Smith G. Pharmacokinetics of single-dose i.v. morphine in normal volunteers and patients with end-stage renal failure. *British Journal of Anaesthesia* 1984; 56: 813–819.
8. Hanning CD, Bogod DG, Smith G, McNeil ME, Graham NB. Further development of a sustained release morphine suppository. *British Journal of Anaesthesia* 1984; 56: 802P.
9. Hanning CD, Smith G, Graham NB, McNeil ME. A sustained release morphine suppository. Abstracts VII European Congress of Anaesthesiology. *Beitrage zur Anaesthesie and Intensivmedizin* 1986; 17: 280.

10. Westerling D, Lindahl S, Anderson KE, Andersson A. Absorption and bioavailability of rectally administered morphine in women. *European Journal of Clinical Pharmacology* 1982; **23**: 59–63.

11. de Blaey CJ, Polderman J. Rationales in the design of rectal and vaginal delivery forms of drugs. In: Ariens P, ed. *Drug Design* Vol 9, New York Academic Press, 1980; 238–266.

Br. J. Anaesth. (1988), **61**, 228–230

ABSORPTION AND BIOAVAILABILITY OF NEBULIZED MORPHINE

J. CHRUBASIK, H. WÜST, G. FRIEDRICH AND E. GELLER

SUMMARY

During anaesthesia seven patients received a bolus of morphine 10 mg injected into the nebulization reservoir placed between the tracheal tube and the anaesthetic circle (IH). Five days after operation the same seven patients received morphine 10 mg i.m. On both occasions, venous blood samples were taken before and every 15 min after administration over 4.5 h for measurement of free morphine immunoreactivity by radioimmunoassay. There was marked individual variation in the serum morphine concentrations produced following each route of administration. The maximum serum morphine concentration following inhaled morphine was approx. six times lower than that after morphine i.m. and the time of occurrence differed significantly ($P < 0.001$). The individual relative bioavailabilities of inhaled morphine varied from 9% to 35%, with a mean of 17%.

Recently it has been shown that postoperative analgesia can be produced and maintained by the inhalation of nebulized morphine [1]. However, the use of this technique in a larger number of patients revealed that pain relief was not always satisfactory. The aim of this study therefore was to evaluate the bioavailability of morphine administered by inhalation.

METHODS AND RESULTS

Following institutional approval and informed written consent, seven patients were studied (two males, five females, mean age 49 (SD 19) yr, mean weight 64 (SD13) kg) during abdominal surgery with 66% nitrous oxide and enflurane in oxygen, plus neuromuscular blockade. All patients suffered from rheumatic diseases requiring chronic non-opioid analgesic treatment. During operation, morphine 10 mg in sodium saline 5 ml was injected into the reservoir of a standard nebulizer (B+P Gmbh, 5206 Neunkirchen-Seelscheid 2, FRG; particle size approx. 5 μm with an oxygen flow of 5 litre min^{-1}) which was placed between the tracheal tube and the semi-closed anaesthetic breathing system with soda-lime. Mean nebulization time was 42 (SEM 3.9) min. The lungs were ventilated to achieve normocapnia with a tidal volume of 10 ml/kg body weight and ventilatory rate of 12 b.p.m.

Pain in the early postoperative period was treated with non-morphine analgesia in order to allow almost complete elimination of the morphine given by nebulization (IH). Upon complaint of pain on the 5th day after operation, morphine 10 mg was administered i.m. into the gluteus maximus (IM). Venous blood samples were taken before and every 15 min for 4.5 h after the two morphine administrations for measurement of free morphine immunoreactivity by radioimmunoassay (Diagnostic Products Corporation, Los Angeles, cross reactivity to morphine-3-glucuronide 0.22%).

Pharmacokinetic data were calculated for each subject. Maximum serum concentration of morphine ($C^{\max}$) and the time of its occurrence ($T^{\max}$) were obtained from the serum concentration-time data. The individual elimination half-lives of the terminal phase of the concentration–time curves ($T_{\frac{1}{2}}^{\beta}$) were determined by linear regression analysis when the terminal data points (at least

---

JOACHIM CHRUBASIK*, M.D.; HANS WÜST, M.D.; Department of Anesthesiology, University Hospital, Moorenstrasse 5, 4 Düsseldorf 1, FRG. GERHARD FRIEDRICH, PH.D., M.D., Department of Forensic Medicine, University of Freiburg, 78 Freiburg, FRG. ERAN GELLER, M.D., Department of Anesthesiology, Ichilov Hospital, Tel Aviv University, Tel Aviv, Israel. Accepted for Publication: January 5, 1988.

*Present address, for correspondence: Department of Anesthesiology, University Hospital, Rämistrasse 100, 8091 Zürich, Switzerland.

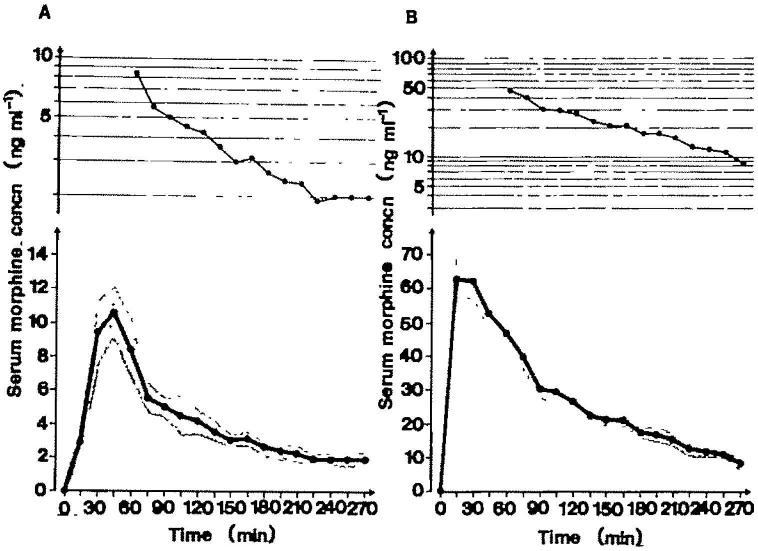


FIG. 1. Mean serum morphine concentrations (SEM) after administration of (A) nebulized morphine 10 mg by inhalation and (B) morphine 10 mg i.m. in the same seven patients.

TABLE I. *Pharmacokinetic details of seven patients who received nebulized morphine 10 mg by inhalation (IH) and i.m. morphine 10 mg (IM) on two separate occasions. %CV = Coefficient of variation*

Patient No.		C^{max} (ng ml^{-1})	T^{max} (min)	$T_{\frac{1}{2}}^{\beta}$ (min)	AUC (ng ml^{-1} min)	F(%)
1	IH	9.0	44.4	144	1009	9.5
	IM	70.2	28.7	143	10631	
2	IH	15.0	56.8	104	1544	15.1
	IM	86.5	21.7	134	10242	
3	IH	21.4	37.3	180	3031	34.6
	IM	56.9	54.6	80	8755	
4	IH	9.8	44.0	123	945	9.7
	IM	101.3	20.4	49	9787	
5	IH	12.1	55.8	142	1617	19.7
	IM	60.4	20.1	105	8198	
6	IH	7.2	39.1	86	899	8.9
	IM	60.9	25.2	150	10090	
7	IH	8.3	40.1	288	1320	18.8
	IM	58.3	25.2	79	7023	
Mean	IH	11.8	45.5	152.4	1480.7	16.6
	IM	70.6	28.0	105.7	9246.6	
%CV	IH	42.0	17.4	44.0	50.1	54.8
	IM	24.1	43.4	36.1	14.1	

three) plotted on a logarithmic axis declined linearly. The area under the curves (AUC) was calculated by the linear trapezoidal method and was extrapolated to infinity by integrating the terminal elimination phase. Individual relative bioavailabilities of the inhaled morphine (F) were calculated by dividing the area under the curve after morphine inhalation (IH) by that after i.m. (IM) administration for each subject.

For statistical analysis, the non-parametric Wilcoxon matched pairs signed rank test was used.

There was marked interindividual variation in the serum morphine concentrations when morphine was given by either inhalation or i.m. injection. In most of the patients receiving nebulized morphine the maximum serum concentration was reached within 45 min, when the mean peak concentration was 10.7 (SEM 1.6) ng ml^{-1}; the maximum serum concentration independent of time was 11.8 (SEM 1.9) ng ml^{-1} (fig. 1A, table I). In contrast, following i.m. administration of morphine a mean serum morphine concentration of 63.5 (SEM 6.2) ng ml^{-1} was reached within 15 min; the maximum serum concentration independent of time was 70.6 (SEM 6.4) (fig. 1B, table I). The maximum serum morphine concentration (C^{max}) after inhalation was approximately six times lower than that after i.m. administration and the times of their occurrence differed significantly ($P < 0.001$).

The relative bioavailability of morphine following inhalation was approximately 9–35%, with a mean of approximately 17%.

COMMENT

Gaensler and colleagues [2] observed that only 7–30% of a nebulized drug inhaled into the lungs was absorbed into the circulation, as at least 50% of the drug is lost on expiration. In addition, loss of drug results from absorption onto equipment and some morphine may be taken up by endothelial cells [3]. Furthermore, patients may swallow drug present in the pharynx.

Our results of the bioavailability of inhaled nebulized morphine support previous observations in which a five-fold difference in serum morphine concentration was found following the inhalation and i.v. administration of morphine given to achieve similar levels of postoperative analgesia[1]. Plateau morphine concentrations of approximately 4 ng ml^{-1} and 20 ng ml^{-1} were achieved within 1 h after commencing inhalation or i.v. treatment, respectively [1]. It is tempting to speculate, therefore, that the mode of analgesia after inhalation of morphine differs from that achieved following other parenteral routes of administration.

The low serum morphine concentrations observed after inhalation of nebulized morphine were found to be associated with fewer side-effects than those seen after i.v. administration. Moreover, it has been found recently that the inhalation of morphine does not increase resting airway resistance [4], which was thought previously to be a severe side-effect of this method.

The great interindividual differences in systemic absorption and the fact that lower serum concentrations of morphine occur after inhalation than following oral [5] or rectal [6] administration suggest that consistent pain relief cannot be anticipated with nebulized morphine and that repeated administration may result in potential hazard.

REFERENCES

1. Chrubasik J, Geller E, Niv, D, Zindler M. Morphine inhalation versus intravenous infusion in pain treatment after abdominal surgery. *Anesthesia and Analgesia*; 1987; **66**: S29.
2. Gaensler EA, Beakey JF, Segal MS. Pharmacodynamics of pulmonary absorption in man. I. Aerosol and intratracheal penicillin. *Annals of Internal Medicine* 1949; **31**: 582–594.
3. Heaton JD, McAnnalley BH, Gardiner TH, Johnson AR. Uptake and release of 14-C-morphine by pulmonary endothelium and cultured pulmonary endothelial cells. *General Pharmacology* 1982; **13**: 105–110.
4. Fuller RW, Choudry N, Karlsson J-A. Inhaled capsicain: effect of opiates. Xth International Congress of Pharmacology, Sydney, Australia, August 23–28, Book of Abstracts, 1987; O 204.
5. Dahlström BE, Paalzow LK. Pharmacokinetic interpretation of the enterohepatic recirculation and first-pass elimination of morphine in the rat. *Journal of Pharmacokinetics and Biopharmaceutics* 1978; **6**: 505–518.
6. Westerling D, Andersson KE. Rectal administration of morphine hydrogel: absorption and bioavailability in women. *Acta Anaesthesiologica Scandinavia* 1984; **28**: 540–543.

Br. J. Anaesth. (1988), **61**, 231–232

INCIDENCE OF SINUSITIS IN PATIENTS WITH NASOTRACHEAL INTUBATION

M. HANSEN, M. R. POULSEN, D. K. BENDIXEN AND
F. HARTMANN-ANDERSEN

SUMMARY

Sinusitis is a complication known to accompany nasotracheal intubation, but its frequency has not been well documented. Twelve patients suffering from cerebral haemorrhage or from cranial trauma and treated with mechanical ventilation were examined for radiological and bacteriological signs of sinusitis with CT-scanning, and cultures of nasal pus discharge. All patients showed radiological signs of sinusitis within 3 days after intubation. They all developed fever, six with a known focus outside the sinuses. There was an even distribution of Gram-negative and Gram-positive bacteria. It is concluded that sinusitis should be considered where fever occurs without known focus in patients with nasotracheal intubation.

Nasotracheal intubation (NTI) is a procedure frequently used in connection with mechanical ventilation. Sinusitis is one of the complications that may arise after intubation. The incidence has been described as ranging up to 26% [1]. Grindlinger and colleagues [2] studied 111 neurosurgical patients. NTI had been performed in 31 and 16 of these developed sinusitis. However, it has been our impression that the incidence is higher than previously stated and, consequently, we have undertaken a prospective study of the incidence of sinusitis following NTI.

METHODS AND RESULTS

The incidence of radiological sinusitis was examined in consecutive patients with cerebral haemorrhage or cranial trauma in whom computerized tomographic scanning (CT-scanning) and NTI had been performed, and who were treated with subsequent mechanical ventilation. It was not possible to obtain informed consent because the patients were unconscious on admission, but the design was approved by the local Ethics Committee.

CT-scans showing thickening of the mucosa without air/fluid levels were considered to be negative. Radiological changes such as air/fluid levels or opacification of the paranasal sinuses were considered positive findings (fig. 1). Assessment of the scans was undertaken by two radiologists, one participating in the study (MP), and controlled by a radiologist otherwise not participating in the study.

The first CT-scan was made either before NTI or immediately after. Patients with positive findings at the first scanning, or patients who were transferred to another hospital before rescanning, were excluded. The remaining patients were rescanned after 1, 2 and 3 days following the intubations, which were performed as emergency procedures.

If there was discharge of pus from the nostril involved, samples were obtained for bacteriological examination.

Of 41 patients in whom CT-scanning and intubation were performed because of cranial trauma or cerebral haemorrhage, 29 were excluded because they had signs of sinusitis at the first scanning or because they were transported to a neurosurgical department for operation before rescanning. Of the 12 remaining patients in the study (median age 39.9 yr, range 4–77), six suffered cerebral haemorrhage and six cranial

---

MORTEN HANSEN, M.D., DIANA K. BENDIXEN, M.D., FLEMMING HARTMANN-ANDERSEN, M.D. (Department of Anesthesiology); METTE R. POULSEN, M.D. (Department of Radiology); Sønderborg Hospital, DK-6400 Sønderborg, Denmark. Accepted for Publication: January 27, 1988.

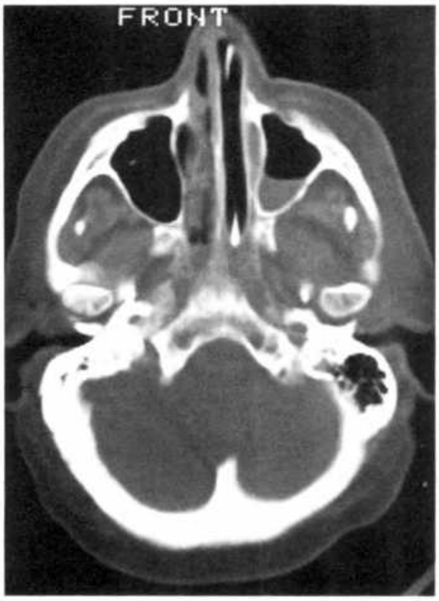


FIG. 1. CT-Scanning 24 h after nasotracheal intubation showing air/fluid level in the right maxillary sinus.

trauma. All showed signs of sinusitis at control scanning 1 or 2 days after intubation. In seven patients, the maxillary sinus on the same side as the NTI was affected primarily. Nine patients developed polysinusitis. In one patient the pattern was atypical, since he first developed opacification of the sinus opposite the intubation, but a nasogastric tube (NTG) was situated on the side of the sinusitis. Nasogastric tubes were inserted in seven patients.

All patients developed fever (temperature > 38.5 °C), six with a known focus of infection outside the sinuses. None of these developed sepsis during the period of investigation. Most of the patients had mildly increased white blood cell counts. Positive cultures of nasal pus discharge were found in seven patients. The cultures consisted mostly of a single predominant species, and with an even distribution of Gram-negative and Gram-positive bacteria.

COMMENT

Sinusitis in connection with NTI is caused by direct irritation followed by oedema and blocking of the ducts in addition to direct obstruction caused by the tube. In this study, we found that all patients showed radiological signs of sinusitis after intubation of 72 h duration.

Seven of the patients also showed clinical signs as discharge of pus around the nasotracheal tube. This incidence is much higher than previously observed. An explanation of this high incidence may be that our patients were exposed to several predisposing factors such as NGT, heavy sedation, supine positioning, immobilization and possibly emergency NTI [2, 3].

The fact that we used CT-scans in all patients may also explain the high incidence. In addition to providing a high diagnostic level of identification (> 90%), CT-scanning makes it possible to evaluate the frontal, sphenoid and ethmoid sinuses. The diagnosis of sinusitis may be made by ordinary x-ray examination using four standard projections. This provides positive identification in 25% of patients. If Water's view is added, identification increases to approximately 90% [1].

The development of sinusitis seems to be a dynamic process since, in most patients, the air/fluid level or opacification was found first on the side where the tube was positioned, and subsequent scannings showed reactions in the other sinuses.

The aim of treatment is primarily to improve the size of the nasal passage (removal of the tube, oral intubation or tracheotomy). These measures seem curative within 48 h in most patients [4]. Topical treatment with decongestants may be temporarily useful. Further treatment comprises administration of antibiotics. Surgical drainage should be considered only in patients in whom conservative treatment is unsuccessful.

It is suggested that the diagnosis of sinusitis should be considered when fever is present without a known cause in patients with nasotracheal intubation.

REFERENCES

1. O'Reilly MJ, Reddick EJ, Black EJ, Carter PL, Erhardt JE, Fill W, Sado A, Klatt GR. Sepsis from sinusitis in nasotracheally intubated patients. *Americal Journal of Surgery* 1984; **147**: 601–604.
2. Grindlinger GA, Niehoff J, Hugehes SL, Humphrey MA, Simpson G. Acute paranasal sinusitis related to nasotracheal intubation of head-injured patients. *Critical Care Medicine* 1987; **15**: 214–217.
3. Kronberg FG, Goodwin WJ. Sinusitis in intensive care unit patients. *Laryngoscope* 1985; **95**: 936–938.
4. Caplan ES, Hoyt NJ. Nosocomial sinusitis. *Journal of the American Medical Association* 1982; **247**: 639–641.

Br. J. Anaesth. (1988), **61**, 233–236

PROLONGED SUXAMETHONIUM-INDUCED NEUROMUSCULAR BLOCKADE ASSOCIATED WITH ORGANOPHOSPHATE POISONING

F. PEREZ GUILLERMO, C. M. MARTINEZ PRETEL, F. TARIN ROYO, M. J. PENA MACIAS, R. ALVAREZ OSSORIO, J. A. ALVAREZ GOMEZ AND C. J. VIDAL

SUMMARY

We report a patient, exposed to Malathion during agricultural work, who suffered a prolonged apnoea after the administration of suxamethonium. He had a normal phenotype ($E_1^u\ E_1^u$), but an extremely low plasma cholinesterase activity. The diagnosis was made by assaying cholinesterase activity and analysing the enzymic components by electrophoresis on polyacrylamide gel slabs. The results indicated that the apnoea was a result of the low activity of plasma cholinesterase induced by Malathion.

Since the introduction of suxamethonium as a neuromuscular blocking agent [1, 2], clinical reports have emphasized the advantage of its short duration of action and its consequent degree of controllability [3, 4]. Suxamethonium produces more complete muscle paralysis of more rapid onset than other drugs—although in some patients prolonged apnoea can occur. Several reasons have been advanced to explain this complication, the most plausible being that the inactivation of suxamethonium may be delayed if the activity of cholinesterase in the plasma (ChE, EC, 3.1.1.8) is less than normal. There is a definite relationship between low ChE activity and prolonged periods of apnoea [5].

The genetic polymorphism of plasma ChE was first described by Bourne, Collier and Somers [6] and Forbat, Lehmann and Silk [7]. Kalow and Genest [8] showed that prolonged apnoea after suxamethonium could be caused by an inherited abnormal ChE which was more resistant to inhibition by dibucaine than the normal enzyme.

Studies of ChE suggest the existence of four autosomal allelic genes at locus E_1, controlling the synthesis of variants of the enzyme: E_1^u (usual), E_1^a (atypical), E_1^f (fluoride resistant) and E_1^s ("silent", not producing cholinesterase activity) [9]. Combination of these genes can produce any one of 10 genotypes at locus E_1. Therefore, homozygotes for the usual gene ($E_1^uE_1^u$) have ChE activity values within the normal range (benzoylcholine hydrolysed = 0.68–1.15 µmol min^{-1}/ml of serum). Heterozygotes for the usual and the atypical or fluoride resistant gene (E_1^a or E_1^f) have moderate ChE activity (0.48–1.11 u. ml^{-1}), whereas those with genotype $E_1^u\ E_1^s$ have about one-half the ChE activity found in homozygotes (0.38–0.87 u. ml^{-1}). Homozygotes for the atypical gene ($E_1^a\ E_1^a$) have very low ChE activity (0.16–0.76 u. ml^{-1}), being very prone to apnoea when treated with suxamethonium, whereas homozygotes for "silent" gene ($E_1^s\ E_1^s$) have no ChE activity and are extremely sensitive [10].

In addition, subjects may have low plasma ChE activity as the result of hepatic disease [11, 12]. The decrease in plasma ChE might be transient, but in some patients it may be permanent, as after prolonged exposure to anticholinesterase agents, the inhibitor being covalently bound to the active site of the enzyme [13–15]. This is demonstrated in the following case report.

F. PEREZ GUILLERMO, M.D.; C. M. MARTINEZ PRETEL, M.D.; F. TARIN ROYO, M.D.; MA. J. PENA MACIAS, M.D.; R. ALVAREZ OSSORIO, M.D.; J. A. ALVAREZ GOMEZ, M.D.; Department of Anaesthesia and Reanimatión, Sta María del Rosell, Alfonso XIII Av., Cartagena, Spain. C. J. VIDAL, B.SC., PH.D., Department of Biochemistry, Faculty of Biology, Espinardo, Murcia, Spain.

Accepted for Publication: October 30, 1986.

Correspondence to C.J.V.

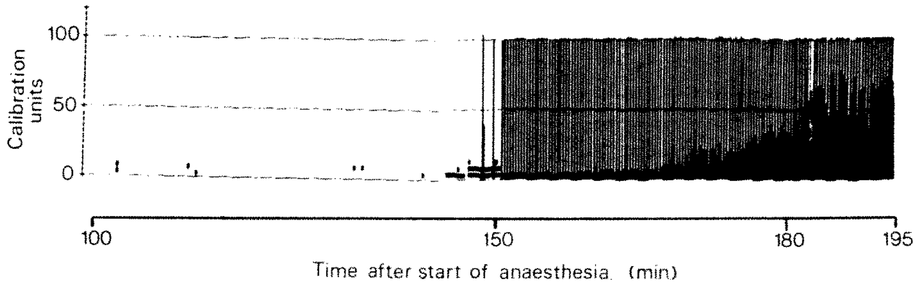


FIG. 1. Slow reversal of suxamethonium-induced neuromuscular blockade in a patient poisoned by exposure to Malathion. Suxamethonium 100 mg was administered.

PATIENT AND METHODS

A 30-year-old male patient (90 kg) entered hospital suffering from acute appendicitis. Both physical examination and routine biochemical data were normal. After i.v. premedication with atropine 1 mg, fentanyl 100 μg and droperidol 5 mg, general anaesthesia was induced with thiopentone 5 mg kg^{-1} i.v. To facilitate tracheal intubation, suxamethonium 100 mg was administered. Anaesthesia was maintained with 67% nitrous oxide in oxygen; analgesia was produced with fentanyl given as necessary, and artificial ventilation was adjusted to maintain normocapnia.

The surgical procedure took 40 min, but the patient remained apnoeic after the initial dose of suxamethonium. Mechanical ventilation was maintained and, 1 h after the end of the operation, an electromyographic recording was obtained (Datex Electromyograph) using surface electrodes over the ulnar nerve. Four supramaximal stimuli (2 Hz for 2 s) were repeated every 20 s. The record revealed evidence of profound block (fig. 1). Spontaneous restoration of neuromuscular activity began 150 min after the start of the anaesthetic. Neuromuscular transmission had recovered to 70% by 180 min after the administration of the suxamethonium, and this was followed by the restoration of spontaneous ventilation. Its adequacy was assessed by spirometry and arterial blood-gas estimation.

Information obtained after questioning the relatives of the patient revealed that he had been working with insecticides during the 3 years before his admission to hospital (3 months per year, March to May). In fact, he came into hospital after being continuously exposed to organophosphate (sometimes inside greenhouses) for 11 weeks. Therefore, we decided to determine the level of ChE activity and the number of isoenzymes present in the serum. Blood samples were collected 3 h after his recovery from operation.

Cholinesterase activity was determined as described by Kalow and Genest [8] using a recording spectrophotometer at 25 °C. The change in light absorbance at 240 nm was followed and the results expressed as benzoylcholine hydrolysed: μmol min^{-1}/ml of serum (u. ml^{-1}). The spectrophotometric method of Ellman and colleagues [16] was also used with butyrylthiocholine as a substrate and the change of light absorbance at 412 nm recorded, the results being expressed as butyrylthiocholine split: μmol min^{-1}/ml of serum (u. ml^{-1}) at 25 °C.

The phenotype of the patient was established by estimation of the dibucaine number [8], fluoride number [17], chloride number [18] and suxamethonium (Scoline) number [19].

Separation of ChE isoenzymes was achieved by means of electrophoresis on prepared concave gradient gels obtained from Pharmacia (Sweden). Gels were in slab form (82 × 82 × 4.9 mm) and consisted of a polyacrylamide concentration gradient running from 2 to 16% w/v. Samples were applied after "pre-running" the gels for 15 min at the voltage used for electrophoresis. Electrophoresis was carried out at 125 V (constant voltage) for about 15 h with a buffer of Tris 88 mol litre^{-1}, borate 82 mmol litre^{-1} and EDTA 3 mmol litre^{-1} (pH 8.3) and at a temperature of 10–15 °C.

The gel was stained according to the procedure of Harris, Hopkinson and Robson [20] with 1% alpha-naphtyl acetate in acetone 3 ml as substrate and Fast red 120 mg in 150 ml of phosphate buffer 0.1 mol litre^{-1}, pH 8. The gels were incubated in the above staining solution for 20–30 min at 37 °C.

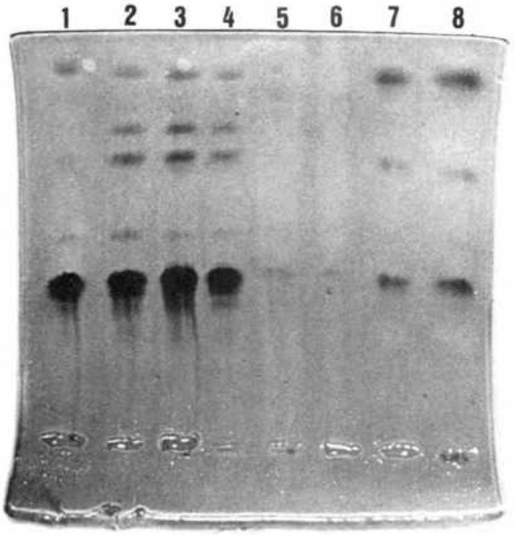


FIG. 2. Electrophoretic patterns of serum cholinesterase isoenzymes. Lanes 2 and 3: sera of individuals with the typical phenotype $E_1^u E_1^u$. Lanes 1, 7 and 8: samples of aged sera from normal individuals $E_1^u E_1^u$. Lane 4: serum of an individual with atypical phenotype $E_1^a E_1^a$. Lanes 5 and 6: serum of the patient poisoned with the organophosphate Malathion.

RESULTS

The electromyographic record shown in figure 1 revealed a depolarizing neuromuscular block with restoration of neuromuscular transmission 180 min after administration of the suxamethonium.

The ChE activities in the patient's serum were 0.3 u. ml^{-1} by the Ellman method (normal range 3.0–9.0 u. ml^{-1}) and 0.05 u. ml^{-1} by the Kalow and Genest procedure (normal range 0.6–1.15 u. ml^{-1} [21]). The phenotype of the patient, after analysis of the ChE inhibition produced by dibucaine, fluoride, chloride and suxamethonium, was considered to be normal ($E_1^u E_1^u$).

Electrophoretic studies of the patient's serum revealed the almost complete absence of bands of ChE activity, whereas the sera of healthy subjects with usual ($E_1^u E_1^u$) or atypical ($E_1^a E_1^a$) genotype contained the normal full range of isoenzymes (fig. 2).

DISCUSSION

In a patient with prolonged apnoea after the administration of suxamethonium and with the electromyograph record obtained here, it could be assumed that the subject exhibited a phenotype $E_1^a E_1^a$ for serum ChE or, alternatively, heterozygote phenotypes of atypical enzyme with genes F or S ($E_1^a E_1^f$ or $E_1^a E_1^s$). However, this was not the case for the serum ChE of our patient, since his phenotype was $E_1^u E_1^u$, as demonstrated by inhibition studies with several agents. Thus the cause of the low ChE concentration has to be a non-genetic modification of enzyme structure. It is well known that organophosphates are extremely toxic, because ChE can be phosphorylated at the active site yielding a phosphoryl-enzyme, which remains inactive and unable to hydrolyse the substrate [22]. Since our patient was subject to prolonged exposure to the action of organophosphates, this appeared to be reason for such a decrease in serum ChE activity.

Although Malathion is one of the safest and least toxic of insecticides in man, being rapidly broken down by esterases to relatively inactive compounds within minutes, it might be that the patient suffered from acute poisoning as a result of the prolonged exposure without any kind of protection (he used to smoke without washing his hands; he did not wear a mask for protection). On the other hand, it is known that commercial insecticides may contain a mixture of different toxic compounds and the possibility that some other organophosphate compound, contaminant or impurity was the primary agent instead of Malathion cannot be ruled out.

The electrophoretic studies confirmed our assumption of a direct relationship between a low serum ChE concentration and organophosphate poisoning, since the serum of healthy subjects yielded the normal set of ChE isoenzymes. It could be argued that the patient's ChE belonged to an unusual type of enzyme which was unable to transform the alpha-naphtyl acetate used as substrate in the staining solution, but this can be ruled out since it is well established that the atypical ChE has even more affinity for this compound than the usual enzyme [23]. On the other hand, the behaviour of neuromuscular transmission, which showed only depolarizing block during the full period of apnoea and recovery (with absence of fade of train-of-four response), might be the result of very low ChE activity in the subject's serum, this being of the usual kind instead of an atypical ChE. It is noteworthy that recovery of patients exhibiting apnoea and displaying a homozygous genotype $E_1^a E_1^a$ treated with Cholase [24] after 30 min of suxamethonium administration, was similar to that reported above.

The slow re-establishment of neuromuscular activity can be explained by the parallel removal of the suxamethonium from blood, endplate and unspecific receptors through redistribution, urinary excretion and alkaline hydrolysis. Our patient is similar to that reported by Baraka, Cava and Jaoude [25], who described prolonged neuromuscular blockade after an acute overdose of Parathion. In that patient they found that administration of half a normal dose of suxamethonium produced an apnoea of 45 min. If they had administered a normal dose it is likely they would have seen an apnoea in the same range as that described here.

Our patient had no apparent impairment or defect of neuromuscular function before anaesthesia, although his plasma cholinesterase concentration was only 3–10% of normal and the duration of action of suxamethonium was prolonged. These findings may reflect the relative selectivity of organophosphorus insecticides for plasma cholinesterase (rather than acetylcholinesterase). Therefore, it should be emphasized that symptomless patients with subclinical exposure to organophosphorus insecticides may develop suxamethonium apnoea. Thus, it may be advisable to screen the ChE in the serum of patients working in agriculture, where they are very often exposed to anticholinesterase agents.

REFERENCES

1. Castillo JC, de Beer EJ. Neuromuscular blocking action of succinylcholine (diacetylcholine). *Journal of Pharmacology and Experimental Therapeutics* 1950; **99**: 458–464.
2. Thesleff S. Pharmacologic and clinical experiments with succinylcholine iodide. *Nordisk Medicin* 1951; **46**: 1045.
3. Foldes FF, Rhodes DH jr. Role of plasma cholinesterase in anesthesiology. *Anesthesia and Analgesia* 1953; **32**: 305–318.
4. Wilson WP, Novill WK. Succinylcholine chloride in electroshock therapy. *Archives of Neurology and Psychiatry* 1954; 71: 122–127.
5. Evans FT, Gray PWS, Lehman H, Silk E. Sensitivity to succinylcholine in relation to serum cholinesterase. *Lancet* 1952; **1**: 1229–1230.
6. Bourne JG, Collier HOJ, Somers GF. Succinylcholine (succinoylcholine). Muscle relaxant of short action. *Lancet* 1952; **1**: 1225–1229.
7. Forbat A, Lehmann H, Silk E. Prolonged apnoea following injection of succinylcholine. *Lancet* 1953; **2**: 1067–1068.
8. Kalow W, Genest N. A method for detection of atypical forms of human serum cholinesterase: determination of dibucaine numbers. *Canadian Journal of Biochemistry and Physiology* 1957; **35**: 339–346.
9. Motulsky AG. Progress in medical genetics. In: *Pharmacogenetics*. Steinburg AG, Bearn AG, eds. Grune and Stratton, New York and London, 1964; 49–74.
10. Liddell J, Lehmann H, Silk E. A silent pseudocholinesterase gene. *Nature (London)* 1962; **193**: 561–562.
11. Vorhaus LJ, Scudamore HH, Kark RM. Measurement of serum cholinesterase activity: A useful test in the management of acute hepatitis. *American Journal of Medical Science* 1951; **221**: 140–148.
12. Jorge AD, Sanchez D. Serum levels of C_3 and cholinesterase in various diseases of the liver. *Acta Hepato-Gastroenterologica* 1976; **23**: 19–25.
13. Milthers E, Clemmensens C, Nimb M. Poisoning with Phosphostigmines. Treatment with atropine, pralidoxime methiodide and diacetyl monoxime. *Danish Medical Bulletin* 1963; **10**: 122–129.
14. Quinones MA, Bogden JD, Louria DB, Nakah AE, Hansen C. Depressed cholinesterase activities among farm workers in New-Jersey. *Science of the Total Environment* 1976; **6**: 155–159.
15. Brown JR, Chai FC, Chow LY, Stopps GJ. Human blood cholinesterase activity. *Bulletin of Environmental Contamination and Toxicology* **19**: 1978; 617–623.
16. Ellman GL, Courtney KD, Andres V jr, Featherstone RM. A new and rapid colorimetric determination of acetylcholinesterase activity. *Biochemical Pharmacology* 1961; **7**: 88–95.
17. Harris H, Whittaker M. Differential inhibition of human serum cholinesterase with fluoride: Recognition of two new phenotypes. *Nature (London)* 1961; **191**: 496–498.
18. Whittaker M. The pseudocholinesterase variants. Differentiation by means of sodium chloride. *Acta Genetica (Basel)* 1968; **18**: 556–562.
19. King J, Griffin D. Differentiation of serum cholinesterase variants by succinylcholine inhibition. *British Journal of Anaesthesia* 1973; **45**: 450–454.
20. Harris H, Hopkinson DA, Robson EB. Two-dimensional components in normal human serum. *Nature (London)* 1962; **196**: 1296–1298.
21. Viby-Mogensen J, Hanel HK. A Danish cholinesterase research unit. *Acta Anaesthesiologica Scandinavica* 1977; **21**: 405–412.
22. Usdin E, ed. Reactions of cholinesterases with substrates inhibitors and reactivators. *International Encyclopedia of Pharmacology and Therapeutics*. Oxford: Pergamon, 1970; 1: 60.
23. Bamford KF, Harris HF. Studies on usual and atypical serum cholinesterase using alpha-naphtyl-acetate as substrate. *Annals of Human Genetics* 1964; **27**: 417–425.
24. Viby-Mogensen J. Succinylcholine neuromuscular blockade in subjects homozygous for atypical plasma cholinesterase. *Anesthesiology* 1981; **55**: 429–434.
25. Baraka A, Cava L, Jaoude CA. Atracurium *v.* suxamethonium in a case of organophosphorus poisoning. *British Journal of Anaesthesia* 1984; **56**: 673–674.

Br. J. Anaesth. (1988), **61**, 237–242

CORRESPONDENCE

COMPONENTS OF ANAESTHESIA

Sir,—We would like to comment on two important questions raised in the excellent editorial by Prys-Robers [1]. Prys-Roberts doubts (and we agree) that the dose–effect relationship demonstrated for various pharmacological effects of general anaesthetics may be used to predict their basic effect: prevention of conscious perception of a noxious stimulus. However, pharmacological effects, regarded as the basic components of anaesthesia (unconsciousness, blockade of motor response and suppression of autonomic responses to noxious stimulation) may have different interrelationships, and therefore the index of one of the components may not be a reliable indicator of another component. Figure 1 demonstrates that the relationship and even the ranked order of the components of anaesthesia are such that prediction for one component of anaesthesia based on the results obtained with another component is different between agents. With a combination of several drugs, the relationship between the components becomes even more complicated [2].

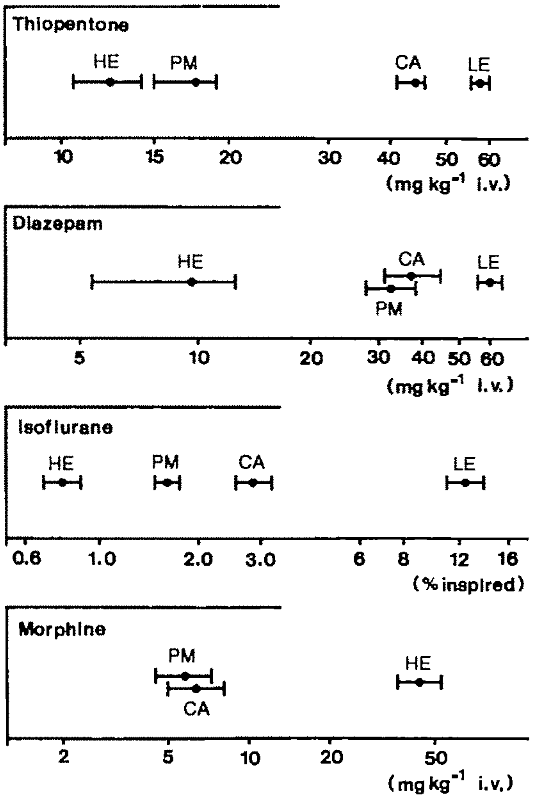


FIG. 1. Median effective doses of thiopentone, diazepam, isoflurane and morphine for different end-points of anaesthesia in rats. HE = ED$_{50}$ for hypnotic effect (loss of the righting reflex). PM = ED$_{50}$ for blockade of purposeful movement response to noxious stimulation (equivalent of MAC). CA = ED$_{50}$ for suppression of cardiac acceleration response to noxious stimulation. LE = ED$_{50}$ for lethal effect (LD$_{50}$). Horizontal lines = 95% confidence limits. Data from references [4–6].

The second question is related to the definition of anaesthesia. Prys-Roberts rejects the notion of components of anaesthesia. He defines anaesthesia as a drug-induced unconsciousness when the patient neither perceives nor recalls noxious stimulation. He states that "all other attributes of anaesthetics, the drugs which produce the state of anaesthesia, can be classed as alternative pharmacological properties of the drugs, and not as components of the state of anaesthesia." In the definition of general anaesthesia suggested by Holmes in 1846, the complex of effects provided by a single inhalation anaesthetic was named after one most important effect: unconsciousness that prevents perception of pain. When it became obvious that some of the effects of inhalation anaesthetics can be induced more selectively with other drugs, the concept of components of anaesthesia emerged [3]. As a result, some of the components of anaesthesia could not strictly fit the initial definition. The best example is muscle relaxation: when induced by a general anaesthetic, it is regarded as a component of anaesthesia, but when it is induced by a peripherally acting muscle relaxant, we doubt if it may be termed a component of anaesthesia. Similarly, we may regard psychological detachment, complete analgesia, and amnesia achieved by a combination of specific drugs (neurolept-analgesia) as a substitute for unconsciousness. This does not contradict Woodbridge's concept of components of anaesthesia [3]. He indicated in his table of four components that mental block implies "ataraxia, or amnesia, or sleep."

Can the combination of complete analgesia and amnesia be regarded as anaesthesia consisting of two components? Probably yes. The requirements for different operations/patients can be different, dictating appropriate combinations of components of anaesthesia. Unconsciousness may not necessarily be "the most important" component. In our opinion, all separate effects used to protect the patient from the trauma of surgery should be termed components of anaesthesia, induced selectively by several drugs or unselectively by one drug. They may not fit the strict definition of anaesthesia, but they do reflect appropriate components of anaesthetic management. Our use of words is often not very precise and, at present, we do not see any need to reconcile the contradiction between the initial definition of anaesthesia with its new meaning by restricting this meaning: anaesthesia should include all of its components, even muscle relaxation.

I. Kissin
S. Gelman
Birmingham, Alabama

REFERENCES

1. Prys-Roberts C. Anaesthesia: a practical or impractical construct? *British Journal of Anaesthesia* 1987; **59**: 1341–1345.
2. Kissin I, Gelman S. Three components of anesthesia: One more reason to accept the concept. *Anesthesia and Analgesia* 1987; **66**: 98.
3. Woodbridge PD. Changing concepts concerning depth of anesthesia. *Anesthesiology* 1957; **18**: 536–550.
4. Kissin I, Kerr CR, Smith LR. Assessment of anaesthetic action of morphine and fentanyl in rats. *Canadian Anaesthetic Society Journal* 1983; **33**: 623–628.
5. Kissin I, McGee T, Smith LR. The indices of potency for intravenous anaesthetics. *Canadian Anaesthetic Society Journal* 1981; **28**: 585–589.
6. Kissin I, Morgan PL, Smith LR. Comparison of isoflurane and halothane safety margins in rats. *Anesthesiology* 1983; **58**: 556–561.

SUXAMETHONIUM MYALGIA

Sir,—We were very interested in the article by O'Sullivan, Williams and Calvey [1] relating to suxamethonium myalgia. We would, however, challenge the validity of the deduction that pretreatment with suxamethonium is not effective in ameliorating myalgia, because of the time relationship of 45 s which was used in the study between pretreatment and administration of suxamethonium.

It is generally accepted that, to be effective, pretreatment with a non-depolarizing neuromuscular blocking agent must be given 2–3 min before suxamethonium [2], whereas pretreatment with suxamethonium must be "immediately prior to the full relaxant dose of suxamethonium" [3]. This discrepancy arises because of the different pharmacokinetics of the two groups of drugs. Our clinical experience convinces us that correctly timed pretreatment with suxamethonium, or its very slow administration (over a period of 10 s significantly reduces the incidence and severity of suxamethonium myalgia.

J. S. Mather
N. P. Carter
Birmingham

REFERENCES

1. O'Sullivan EP, Williams NG, Calvey TN. Differential effects of neuromuscular blocking agents on suxamethonium-induced fasciculations and myalgia. *British Journal of Anaesthesia* 1988; **60**: 367–371.
2. Glauber D. Incidence and severity of muscle pains after suxamethonium when preceded by gallamine. *British Journal of Anaesthesia* 1966; **38**: 541.
3. Mather JS. Suxamethonium without pains. *Anaesthesia* 1979; **34**: 918.

Sir,—We were interested in the comments of Drs Mather and Carter. We consider that there is little or no definitive evidence that the time interval between pretreatment with suxamethonium and administration of the subsequent dose is of critical importance. In his original description of the technique, Baraka [1] used a latent period of 45–60 s; a similar interval has been used by most subsequent authors, including ourselves [2–5]. We would accept that this technique does not appear to modify postoperative myalgia, but remain unconvinced that the shorter time interval used by Drs Mather and Carter (a difference of approximately 30 s) is of crucial importance. Although it has been suggested that the incidence of muscle pain may be reduced by the slow injection of suxamethonium [6], this has not been confirmed by other authors [7].

We are unable to understand the reference to the different pharmacokinetics of suxamethonium and non-depolarizing blockers. As far as we are aware, the pharmacokinetics of suxamethonium have not been studied, since its plasma concentration cannot be determined reliably.

Finally, although it is often stated that pretreatment with a non-depolarizing neuromuscular blocker must be given 2–3 min before suxamethonium in order to be effective, our data suggest that a shorter time interval may be adequate.

E. P. O'Sullivan
N. E. Williams
T. N. Calvey
Liverpool

REFERENCES

1. Baraka A. Self-taming of succinylcholine-induced fasciculations. *Anesthesiology* 1977; **46**: 292–293.
2. Brodsky JB, Brock-Utne JG. Does "self-taming" with succinylcholine prevent postoperative myalgia? *Anesthesiology* 1979; **50**: 265–267.
3. Wilson DB, Dundee JW. Failure of divided doses of succinylcholine to reduce the incidence of muscle pains. *Anesthesiology* 1980; **52**: 273–275.
4. Masey SA, Glazebrook CW, Goat VA. Suxamethonium: a new look at pretreatment. *British Journal of Anaesthesia* 1983; **55**: 729–733.
5. O'Sullivan EP, Williams NE, Calvey TN. Differential effects of neuromuscular blocking agents on suxamethonium-induced fasciculations and myalgia. *British Journal of Anaesthesia* 1988; **60**: 367–371.
6. Foldes FF. Factors which alter the effects of muscle relaxants. *Anesthesiology* 1959; **20**: 464–504.
7. White DC. Observations of the prevention of muscle pains after suxamethonium. *British Journal of Anaesthesia* 1962; **34**: 332–335.

ASSESSMENT OF THE DATEX RELAXOGRAPH IN ACCESSORY NERVE STIMULATION

Sir,—Since the report of Schumm and Stöhr [1] we have frequently observed that stimulation of the accessory nerve is useful, not only in the assessment of myasthenia gravis, but also in the assessment of neuromuscular transmission in anaesthetized patients. The method is sensitive and reliable, and we decided to use it with the Datex Relaxograph in the "train-of-four" mode of stimulation.

Stimulating electrodes were placed just behind the sternocleidomastoid muscle, the exploring electrode 4 cm dorsal to the edge of trapezius muscle, the indifferent electrode above the clavicle and the ground electrode medial to the indifferent electrode.

Since our purpose was to monitor the *trend* of neuromuscular transmission for prolonged periods (rather than to detect absolute values) we used only submaximal stimuli with intensities of current that are selected on the basis

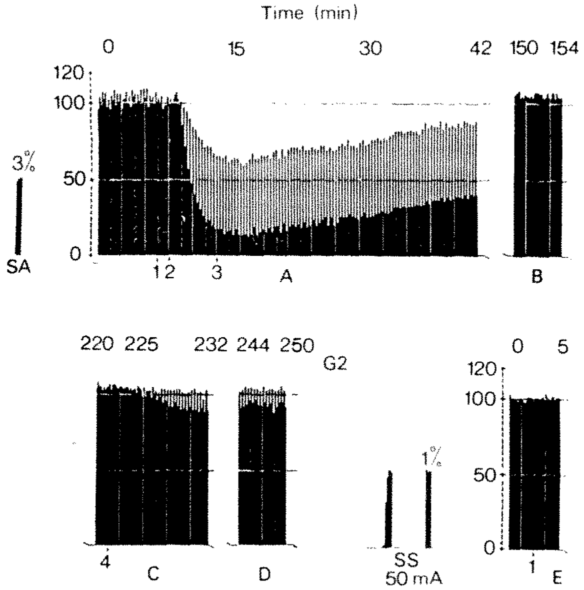


FIG. 1. Traces obtained from a 59-yr-old patient undergoing general anaesthesia for embolization of spinal arteriovenous dural fistula. A–D: Accessory nerve stimulation (20 mA). 1 = Pancuronium 4 mg; 2 = induction with barbiturate, nitrous oxide, isoflurane; 3 = intubation; 4 = pancuronium 0.5 mg. E: Supramaximal stimulation (50 mA) of ulnar nerve after recalibration at time 253 min. 1 = Discontinuation of nitrous oxide and isoflurane. SA = Stimulus artefact. SS = Supramaximal stimulus. G2 = Gain = 2 calibration values.

of the patient's tolerance in the range of 10–30 mA. The quality of the responses so obtained was then intermittently controlled by supramaximal stimulation with a Medelec EMG (MS 92a).

An example recording is presented in figure 1, obtained from a 59-yr-old patient undergoing general anaesthesia for embolization of a spinal arteriovenous dural fistula.

Premedication was with diazepam and atropine. The procedure was explained to the patient and correct positioning of electrodes sought by the use of the Medelec EMG. Submaximal (20 mA) stimulation of the left accessory nerve was initiated 5 min before the induction of anaesthesia. We wanted to be sure that the intensity of current was sufficiently low to be well tolerated by the *awake* patient and sufficiently high to be well accepted by the instrument (without drifting or other artefacts).

It should be noted that, after the small dose of pancuronium (0.5 mg), a response to the neuromuscular blocker was present in the trapezius muscle only and not in the abductor digiti minimi (in spite of supramaximal stimulation). Such a difference was confirmed by the Medelec EMG after supramaximal repetitive stimulation at 2 Hz at time 239 min: in trapezius muscle the 4th response was 68 % of the first; in the abductor digiti minimi it was 92 % (not shown in the figure).

We cannot say whether this difference was attributable to the lower temperature of distal muscles [1] or to the lower "safety margin" of proximal ones [2].

We think, however, that the method is so sensitive and so well tolerated by most patients that it can be recommended especially in patients in whom *postoperative* treatment could impair neuromuscular transmission or in those in whom it is important to evaluate the neuromuscular effects of drugs such as edrophonium or treatment such as plasmaphoresis.

F. FIACCHINO
M. BRICCHI
M. MONTOLIVO
C. FERRAZZA
V. BORRONI
Milan

REFERENCES

1. Schumm F, Stöhr M. Accessory nerve stimulation in the assessment of myasthenia gravis. *Muscle and Nerve* 1984; 7: 147.
2. Stälberg E. Clinical electrophysiology in myasthenia gravis. *Journal of Neurology, Neurosurgery and Psychiatry* 1980; **43**: 622.

RAPID SEQUENCE INDUCTION IN PREGNANCY-ASSOCIATED HYPERTENSION—THE ROLE OF MAGNESIUM

Sir,—Lawes and colleagues [1] have made a commendable attempt at answering the difficult problem of controlling cardiovascular disturbance during tracheal intubation in patients suffering from severe pregnancy-induced and pregnancy-aggravated hypertension. In a study of this nature it is inevitable that many variables may make interpretation of the data difficult, and their argument that a control group is not justifiable in this condition is reasonable.

Nevertheless, two groups of patients are clearly discernible among those presented: those who received magnesium sulphate before anaesthesia (nine patients), and those who did not (15 patients). The authors state that magnesium sulphate is a standard form of therapy in their unit, but do not explain on what basis these nine patients were selected to receive magnesium. Presumably this was an obstetric decision alone. Magnesium has significant cardiovascular effects, including reductions in peripheral vascular resistance and, to a lesser extent, arterial pressure. Serum magnesium concentrations of 2.5–4 mmol litre^{-1} inhibit the release of catecholamines in response to stress and can reduce the pressor response to intubation.

From the data presented, it can be calculated that the mean increase in systolic arterial pressure was 10.0 (SD 25.9) mm Hg in the magnesium pretreated group, and 22.7 (SD 31.2) mm Hg in the group which did not receive magnesium. Although the difference between these groups does not reach statistical significance, possibly because of the relatively small size of the samples and the large standard deviations, the possibility cannot be excluded that magnesium pretreatment played an important role in the control of cardiovascular instability. Furthermore, only one of nine magnesium-treated patients was in the unmodified response group, whereas four of 15 who did not receive magnesium were in this category. The one patient was one of only two with severe hypertension (mean arterial pressure before entry into the study 157 mm Hg) who did not receive a vasodilator before induction.

Magnesium has been shown to obtund the pressor response to intubation in hypertensive pregnant patients [2]. As administration of fentanyl and the use of magnesium may inhibit the release of catecholamines by different mechanisms, it seems likely that the two drugs used in conjunction would enhance cardiovascular control. It is possible, therefore, that the favourable results reported by Lawes and colleagues [1] were at least partly the result of a combination of fentanyl, droperidol and magnesium, and not the fentanyl–droperidol combination alone. It is a pity that serum magnesium concentrations were not available at the time of intubation.

M. F. M. James
Johannesburg

REFERENCES

1. Lawes EG, Downing JW, Duncan PW, Bland, Lavies N, Gane GAC. Fentanyl–droperidol supplementation of rapid sequence induction in the presence of severe pregnancy-induced and pregnancy-aggravated hypertension. *British Journal of Anaesthesia* 1987; 59: 1381–1391.
2. Cork RC, James MFM. Magnesium pre-treatment at C-section for pregnancy induced hypertension. *Anesthesia and Analgesia* 1985; 64: 202.

LONG TERM USE OF THE VOCALAID TRACHEOSTOMY TUBE FOR TRACHEAL TOILET

Sir,—I have read the letter by Dr Manara and Park [1] on the use of the Vocalaid tracheostomy tube for tracheal toilet, and feel that further comment is required.

With large volume–low pressure cuffs, it is possible to seal the airway with extremely low expiratory cuff pressures. However, resting intracuff pressures as low as 1 kPa do not necessarily protect against aspiration, particularly as these large volume cuffs are prone to produce longitudinal foldings of the cuff material, forming channels through which liquid may travel down the trachea [2, 3]. There is no reference in the letter regarding the exact intracuff pressure used in their patient. Although it is prudent not to allow food and saliva to accumulate above the cuff in patients with bulbar paralysis and patients with tracheal tubes, by incorporating an aspiration channel just above the cuff, a correct design and size of large volume–low pressure cuff inflated to optimal intracuff pressure would eliminate any aspiration hazard. It is, therefore, essential to use the correct size of cuff with optimal diameter and circumference, which will effect a seal, with minimal infolding of excess cuff material. To prevent aspiration with large volume–low pressure cuffs, the lateral wall pressure should exceed maximum hydrostatic pressure that can be generated by a column of liquid above the cuff. It is recommended to maintain intracuff pressure during expiration between 2.5 and 3 kPa to provide a safe two-way seal against both air leakage and aspiration [4].

S. Mehta
Burnley

REFERENCES

1. Manara AR, Park GR. Long term use of the Vocalaid tracheostomy tube for tracheal toilet. *British Journal of Anaesthesia* 1987; 59: 523–524.
2. Bernhard WN, Cottrell JE, Shivkumaran C, Patel K, Yost L, Turndorf H. Adjustment of intracuff pressure to prevent aspiration. *Anesthesiology* 1979; 50: 363.
3. Mehta S. Performance of low-pressure cuffs. *Annals of the Royal College of Surgeons of England* 1982; 64: 54.
4. Mehta S, Mickiewicz M. Pressure in large volume, low-pressure cuffs: its significance, measurement and regulation. *Intensive Care Medicine* 1985; 11: 267–272.

Sir,—We would like to thank Dr Mehta for his interest in our report and agree with his comments about low pressure–high volume cuffs and pulmonary aspiration.

The reason we did not include intracuff pressure in our report is because we did not measure it. The cuff was inflated in this patient until an airtight seal was achieved. The size of the Vocalaid used was carefully chosen to avoid longitudinal folds in the cuff and explains why a smaller than usual tracheostomy tube was used in an adult male. It is possible that longitudinal folds of the cuff material were still present in our patient despite this precaution, but pulmonary aspiration was prevented by the regular aspiration of a suction channel above the cuff, preventing the accumulation of food or saliva.

While measuring intracuff pressure is highly desirable, for the reasons Dr Mehta states, it is neither a practical nor a feasible proposition in a patient being looked after long term by different nurses, both at home and while travelling abroad. Presented with this patient, it was essential to keep things simple yet effective. This aim was achieved by our use of the Vocalaid tracheostomy tube as described, since the patient has not developed any clinical or radiological evidence of pulmonary aspiration over a 2-year period.

G. R. Park
A. R. Manara
Cambridge

BRADYCARDIA FOLLOWING VECURONIUM

Sir,—In their paper entitled "Vecuronium induced bradycardia following induction of anaesthesia with etomidate or thiopentone, with or without fentanyl" [1], Inoue and his colleagues claimed that vecuronium 0.112 mg kg^{-1} i.v. causes bradycardia, and that its maximal effect on heart rate develops 20–30 min after administration. It is difficult to understand how it is possible that the maximal effects of vecuronium, which has a mean distribution half-life of less than 15 min [2], develops in 20–30 min in an organ such as the heart which has an excellent blood supply, whereas the maximal neuromuscular effect of a similar dose of vecuronium develops in less than 6 min [3]. Furthermore, what is the explanation of the finding, in their "pancuronium" group at 20 and 30 min and in their "suxamethonium" group at 10, 20 and 30 min, that heart rates were also significantly slower than control. It is well known, in subjects inhaling room air (21% oxygen), that sleep alone, without the administration of any drug, reduces heart rate and systolic arterial pressure [4, 5]. In subjects premedicated with morphine and diazepam, subsequently anaesthetized with a variety of drugs including enflurane, and allowed to sleep peacefully, without any external stimulation, while breathing 40–50% oxygen, it is conceivable that the changes in heart rate and arterial pressure would be similar to those observed in this study after the administration of vecuronium.

The validity of this assumption could be tested by performing tracheal intubation in a group of similarly premedicated and anaesthetized subjects (not necessarily cardiac patients), after topical anaesthesia of the pharynx and larynx without previous administration of vecuronium, and observing heart rate and arterial pressure in the ensuing 30 min. Until such studies have been performed, the only justifiable conclusion is that vecuronium has no chronotropic or other cardiovascular effect and, therefore, it does not antagonize the bradycardia caused by other drugs or sleep.

F. F. FOLDES
New York

REFERENCES

1. Inoue K, El-Banyosy A, Stolarski L, Reichelt W. Vecuronium-induced bradycardia following induction of anaesthesia with etomidate or thiopentone, with or without fentanyl. *British Journal of Anaesthesia* 1988; **60**: 10–17.
2. Cronnelly R, Fisher DM, Miller RD, Gencarelli P, Nguyen-Gruenke L, Castagnoli N jr. Pharmacokinetics and pharmacodynamics of vecuronium (Org-NC45) and pancuronium in anesthetized humans. *Anesthesiology* 1983; **58**: 405–408.
3. Foldes FF, Nagashima H, Boros M, Tassonyi E, Fitzal S, Agoston S. Muscular relaxation with atracurium, vecuronium and Duador under balanced anaesthesia. *British Journal of Anaesthesia* 1983; 55: 97S–104S.
4. Kleitman N. *Sleep and Wakefulness*. Chicago and London: University of Chicago Press, 1963; 552.
5. Baust W, Bohnert B. The regulation of heart rate during sleep. *Experimental Brain Research* 1969; 7: 269–180.

TRANSFER FROM RECOVERY ROOM TO WARD

Sir,—From the anaesthetic point of view a patient can be discharged from the recovery room: (1) when he is able to maintain adequate alveolar ventilation and can clear his airway; (2) when he is awake, alert, well orientated in space and time, and can make his wants and needs known; (3) if he is able to maintain adequate tissue perfusion, without continuous monitoring and support of his cardiovascular system; patients with an unstable cardiovascular system should not be moved.

From the surgical point of view, if the patient is not expected to need close surgical surveillance he can be transferred. A trained nurse preferably should accompany the patient whenever necessary.

The author's recovery score (table I) assesses three physical signs: "A, B, C of recovery" (Airways, Behaviour, Consciousness). A score of 8 is the minimum for discharge from the recovery room in most instances.

We have assessed this score in more than 2000 patients aged from 1 to 80 yr and of both sexes. We found and concluded that this score is an effective guide to the recovery of patients and to the time for discharge to the wards. There was no residual effect of anaesthesia. The patients were awake, well orientated and could make their wants and needs known to nursing staff in the wards. This A, B, C scoring system is simple and helpful to junior staff.

M. SALEM
Rawalpindi

TABLE I. *Postanaesthetic "A, B, C of recovery" score. Patient is fit to leave the recovery room when score is at least* 8

	Score for response			
Physical signs	3	2	1	0
Airway	Patient can cough or cry	Maintains clear airway without holding the jaw	Holding of jaw needed	Holding of jaw and other measures taken to maintain airway
Behaviour	Patient can lift head	Can open the eyes and show tongue	Some non-purposeful movements	No movements at all
Consciousness	Fully awake, can talk, well orientated	Awake but needs support	Responds to stimuli only	No response

FRESH GAS FLOW REQUIREMENTS WITH THE ADE ANAESTHETIC SYSTEM

Sir,—When evaluating the fresh gas flow requirements of the ADE anaesthetic system, Duncan and colleagues [1] observed a poor correlation between arterial and end-tidal carbon dioxide tensions, but did not present an explanation. One possibility depends upon the design of capnometer used; some display absolute $P\text{CO}_2$ while others display the difference between inspired and expired gas. When rebreathing occurs, the latter types display a decreasing "$P\text{CO}_2$", with no indication that inspired $P\text{CO}_2$ is greater than zero. Could this have been the case? Presumably the occasions when $P\text{E}'_{\text{CO}_2}$ was greater than Pa_{CO_2} represent inherent errors of sampling, or the influence of nitrous oxide on analysers and the "concentration effect" in the lung; these errors should not be greatly influenced by fresh gas flow. Did the authors observe a better correlation in the higher gas flow group, or have they some other explanation? Would they not agree that, when using an anaesthetic system which permits rebreathing, the ideal capnometer would display inspired and expired $P\text{co}_2$ values?

G. C. Fisher
Birmingham

REFERENCE

1. Duncan PW, Lawes RG, Bland B, Downing JW. Fresh gas flow requirements using the ADE anaesthetic system in late pregnancy. *British Journal of Anaesthesia* 1987; 59: 360–363.

Sir,—Thank you for the opportunity to reply to Dr Fisher's letter. The capnometer used displayed both inspired and expired $P\text{co}_2$ and did not re-zero on the concentration of carbon dioxide in the inspired gas.

We too were surprised at the number of patients whose measured Pa_{CO_2} was less than the $P\text{E}'_{\text{CO}_2}$. It seemed unlikely that technical errors alone could account for this reversal of arterial–alveolar carbon dioxide gradients. A literature search revealed that, in 1891, Bohr first described reversal of arterial–alveolar carbon dioxide gradients when high concentrations of carbon dioxide were present in inspired air. This finding has been confirmed using modern methods. The subject has been reviewed by Gurtner [1], who discussed the possible mechanisms by which it was produced.

The occurrence of negative arterial–alveolar carbon dioxide differences has been noted during rebreathing [2, 3] during exercise with rebreathing [4, 5] and without rebreathing [6]. The degree of magnitude of negative arterial–alveolar carbon dioxide differences is related to the degree of hypercarbia [2].

Mapleson E breathing systems, when used as in our study, allow partial rebreathing. Pregnancy causes physiological changes akin to exercise, such as increased cardiac ouput, increased ventilation, increased oxygen consumption and carbon dioxide production. These factors could explain the negative arterial–end-tidal carbon dioxide differences we found. The higher incidence of negative arterial–end-tidal carbon dioxide differences in the lower fresh gas flow groups could reflect both increased rebreathing and increasing hypercarbia.

As stated in the paper, Pa_{CO_2} did not correlate well with $P\text{E}'_{\text{CO}_2}$, but the r values were almost identical in both high and low gas flow groups.

I would agree that, when using rebreathing systems, it is essential to use a capnometer which does not zero on the inspired $P\text{co}_2$. However, the occurrence of variable and reversible arterial–end-tidal carbon dioxide gradients render indirect measurement of Pa_{CO_2} in rebreathing systems problematic.

P. W. Duncan
Preston

REFERENCES

1. Gurtner G. Can alveolar $P\text{co}_2$ exceed pulmonary end-capillary CO_2? *Journal of Applied Physiology* 1977; **43**: 323–326.
2. Gurtner G, Traystman RJ. Gas-to-blood $P\text{co}_2$ differences during severe hypercapnia. *Journal of Applied Physiology* 1979; 47: 67–71.
3. Steinbrook RA, Fencl V, Gabel RA, Leith DE, Weinberger SE. Reversal of arterial-to-expired CO_2 partial pressure differences during rebreathing in goats. *Journal of Applied Physiology* 1983; 55: 736–741.
4. Jones NL, Campbell EJM, Edwards RHT, Wilkoff WG. Alveolar-to-blood $P\text{co}_2$ differences during rebreathing in exercise. *Journal of Applied Physiology* 1969; 27: 356–360.
5. Jones NL, Robertson DG, Kane JW, Campbell EJM. Effect of $P\text{co}_2$ level on alveolar–arterial $P\text{co}_2$ difference during rebreathing. *Journal of Applied Physiology* 1972; 32: 782–787
6. Whipp BJ, Wossermann K. Alveolar–arterial gas tension differences during graded exercise. *Journal of Applied Physiology* 1969; 27: 361–365

Br. J. Anaesth. (1988), **61**, 243–245

BOOK REVIEWS

Current European Anaesthesiology 1987. Edited by R. M. Jones. Published by John Wiley & Sons, Chichester. Indexed; not illustrated. Price £45.

Current European Anaesthesiology is the yearbook of the European Academy of Anaesthesiology. It is a *pot pourri* of paper synopses, written by the authors, each accompanied by one or more "comments" by authorities selected by the editors. Most reviewers are Academicians drawn, quite literally, from all corners of Europe.

Many of the papers are familiar, and the comments appreciative. As the pages are turned, a year of publications is refreshed in the reader's mind. Worthwhile reading. However, the book does have its moments.

For instance, Richard and colleagues report the use of vecuronium infusions for renal transplantation. Unexceptional enough, but the reviewer (Vourc'h, Paris) comments "Why the authors used pyridostigmine rather than neostigmine is hard to tell but they cannot be blamed for it". This reviewer wonders why not.

Those with stronger tastes might read Dr Boidin's "Can Etomidate cause an Addisonian crisis?" Twelve adult patients undergoing major abdominal surgery were studied in two groups. One group was given etomidate infusions throughout surgery, presumably with the intention of answering the question in the title. The patients given etomidate developed pathologically low serum cortisol concentrations during the postoperative period and these were corrected after the study period ended. Furthermore, four of the six patients given etomidate suffered serious late complications, including wound dehiscence and coagulopathies. In comment, Professor Frei (Basel) wonders why no ethical approval or consent was obtained, and suggested that the study was neither ethical nor necessary. Undoubtedly, the Yearbook will have achieved its prime objective: many more anaesthetists will have read the original article (including this reviewer) than would otherwise have been the case; if only to decide for themselves.

Some synopses are very informative, reminding the reader of important papers he has missed. For instance, Hedenstierna and colleagues showed in eight patients, using multiple inert gases, vascular pressures, thermal dilution cardiac output *and* CAT scanning, that shunt developing soon after the induction of anaesthesia results from atelectasis in dependent lung zones. The reviewer (D. Scheidegger, Basel) admired the paper. Furthermore, he pointed out that the entire study in each patient had taken more than 1 h and required an anaesthetized transfer from Radiology to the Operating suite before surgery could begin. As he remarked, there could be few centres in the world where such a study could be carried out.

All that in the first 54 pages. The editor (R. M. Jones) has, as usual, done an excellent job in creating just the appropriate mix of the best and the worst material published in the previous year or so. I do wish, however, that he might cast his net a little more widely in search of commentators whose views will interest the reader.

C. J. Hull

Aspects of Recovery from Anaesthesia. Edited by I. Hindmarch, J. G. Jones and E. Moss. Published by J. Wiley & Sons, Chichester. Pp. 176; illustrated; indexed. Price £23.50.

Until the covers of this book are opened, it is not immediately apparent that it represents the proceedings of a meeting held in Leeds and sponsored by a pharmaceutical company. However, this is revealed on page 9, by a list of participants in the discussion who were not contributing authors. Despite this acknowledgement, however, no discussion appear in the text, although the editors provide a short synopsis of verbal exchanges following the last chapter.

The book comprises 15 articles, varying in length from 2¼ pages to a 13-page review of recovery of cognitive and psychomotor function following anaesthesia, accompanied by 38 pages of appendix which tabulates the majority of studies in this field up to 1987. Whilst some articles describe only a single study, others comprise short reviews of certain aspects of recovery, for example morbidity following day case anaesthesia, the use of short acting opioids and their effects on recovery from benzodiazepines, i.v. agents and methods of assessment of psychomotor performance and memory.

This book represents an excellent starting point for those who wish to undertake studies of recovery from anaesthesia and should, therefore, be available for inspection in central libraries. However, few anaesthetists would wish to acquire a personal copy.

G. Smith

Databook of Anaesthesia and Critical Care Medicine. Edited by P. Foster and J. Roelofse. Published by Springer-Verlag, Berlin. Pp. 204; illustrated; indexed. Price DM 42.

This little pocket book is intended to provide a collection of useful data for the anaesthetist and those involved in intensive care. In many respects it is similar to a small pocket book produced by three British authors. However, this booklet emanating from South Africa contains additional information relating to anaesthetic practice, for example risk assessment, porphyria and ISO standards. Somewhat out of context is a description of the objectives of the World Federation of Societies of Anaesthesiology, with a note of names of current officials of the Federation and dates and venues of international congresses.

In general, most of the information contained in this pocket book is extremely useful and will assist the anaesthetist in daily practice. Inevitably, inclusion of other data is a matter of personal opinion; however, one wonders if a table of species variation of MAC is so important as to warrant being carried around in the pocket. There are also obvious drawbacks associated with attempts to deal with complex clinical problems in note form, which thereby assume a semblance of dogma which would not be the authors' intention. An example of the disadvantage of this approach may be seen in the section entitled "Prevention of Regurgitation" which contains: '1. 40° head uptilt…6 do not ventilate'. Experienced anaesthetists may fully appreciate the implications of these statements, but the list would not be sensible advice to hand to the trainee.

Notwithstanding the disadvantages inherent in the compressed note form, this little book contains a vast amount of useful information in a size which may be kept easily in any pocket or briefcase. It can be recommended, although the price is relatively expensive in comparison with its competitors.

G. Smith

Shock and the Adult Respiratory Distress Syndrome. Edited by W. Kox and D. Bihari. Published by Springer Verlag, London. Illustrated. Price £25.00.

This book is published under the general heading of current concepts in critical care. In the preface, the editors point out that the book is a collection of proceedings, plus additional relevant chapters, from a meeting held in March 1986. The aim of this meeting, in Cortina, Italy, was for workers to participate in a workshop in which their latest research and ideas could be discussed in a critical atmosphere.

The book has 18 chapters in five sections dealing with Morphology and Pathogenesis of Acute Lung Injury, Pathophysiology of Shock and ARDS, Aspects of Ventilatory Support, Aspects of Cardiovascular Support and finally Diagnosis and Prognosis of ARDS.

Of the 18 chapters, four are discussions of studies in humans, three from animal investigations, and one contains a theoretical discussion of the use of differences in alveolar to arterial nitrogen partial pressure. The remaining 10 chapters are review or review type articles. These articles vary enormously in quality and breadth of coverage. For example, the opening chapter on the factors affecting fluid flux across endothelium is extremely well written and simplifies a very difficult topic while discussing many current concepts. In contrast, the chapter on the whole body response contains much information and speculation on mechanisms which have been shown subsequently to be of little or no relevance to the pathophysiology of ARDS.

The individual chapters do tend to reflect the individual writer's dogma on each topic and should be read in this light; for example how many people consider the Peclet number when thinking of bulk flow of gas in the airways (I didn't know what a Peclet number was until I read this section!) and do I need to be informed that, in Geneva, they have their own ARDS severity score when most units are using APACHE II or similar generally accepted systems.

The book is extremely well presented and I could not find a typographical error. Additionally, some of the diagrams are worth using for lectures and teaching sessions. The book is easy to read and does have a number of good sections. I would not recommend that anyone with an up to date interest in the subject should buy the book, but they may wish to browse through it in the library.

The place of the book may be suited better to the library shelves of the I.C.U., where the novice S.H.O. or Registrar will obtain some important information in a readable form and may also obtain ideas for research and therapy of a disease process of which the management is still fraught with problems.

D. Royston

Postoperative Pain Control. By J. I. Alexander and R. G. Hill. Published (1987) by Blackwell. Pp. 272; indexed; illustrated. Price £14.95.

"Medical staff could be more involved in the management of pain, not only in the prescription of drugs, but in the monitoring of response and frequent adjustment of dose, timing, or rate of administration to match the varying levels of pain, and in the use of local anaesthetic techniques." This sentence in chapter 9 summarizes the *raison d'être* of this little book, which is described in the preface as a handbook and practical guide. Whether or not it fulfils this description is questionable, since the style of the book is frequently more discursive than didactic.

The first few chapters are short and describe measurement, mechanisms, factors affecting severity, and consequences of postoperative pain. Frequent references to chronic in addition to postoperative pain reflect the authors' interests. The balance of the book as a practical guide is somewhat upset by a lengthy section on pharmacology, comprising four chapters. This is excessive in a purportedly practical, pocket-sized companion; for example, chapter 7 considers drugs associated more usually with chronic pain.

The key chapters are those of Choices in Management, and Regional Anaesthesia. Much of the message of chapter 9 is contained in tables, which constitute almost 50% of the chapter. There is inadequate information on the use of patient-controlled analgesia to enable the enthusiast to embark upon this form of therapy. In contrast, much space is devoted to the technique of lumbar extradural block, which is probably an unnecessary lesson for readers of this book. Similarly, descriptions of regional blocking techniques may be omitted and the reader referred to more comprehensive, illustrated standard texts.

Surprising omissions include the use of small doses of local anaesthetic drug in combination with opioids for extradural administration, and the use of pulse oximetry to monitor respiration after operation. The chapter on problem patients (neonates, day cases, nursing mothers, the elderly and those with increased intracranial pressure or obesity) provides sound practical advice and fulfils the aims of the authors. Unfortunately, postoperative analgesia for day case paediatric patients is not discussed.

The book is well produced and the publishers are to be congratulated on the clear layout. The text is eminently readable, but the lack of textual references may disappoint readers. It will appeal to anaesthetists who require some (re)awakening of their interest in contemporary techniques of postoperative pain control, and may serve to stimulate improvements in this field.

D. Fell

Recovery Room Care, 2nd Edn. Edited by J. S. Israel and T. J. DeKornfeld. Published by Year Book Publishers Inc., Chicago. Indexed; illustrated. Price £34.

In their ingenuous prefaces the editors explain that they have minimized intrusion to authors' style and content and have not attempted to eliminate duplication of themes between chapters. Such liberal attitudes make for easy editing and a longer book than is necessary. Nevertheless, this is a useful source in an area of study in which, otherwise, the material is scattered.

The book is a series of essays. Within each the standard of writing is uniform and the writers seem to identify a target reader. Unfortunately, not all authors are aiming in the same direction. For example, the reader who can warm to the chapter on economic considerations in recovery care and others on specialized physiology (of intracranial pressure control or neonatal caloric expenditure) may not need a special treatise on the main causes of upper airway obstruction in the adult.

In spite of these criticisms, there is no doubt that this book will be useful to teachers and postgraduate students in anaesthesia. The fact that it has progressed to this second, and significantly revised, edition is testimony to that.

D. W. Noble
A. A. Spence

Clinical Anesthesia Procedures of the Massachusetts General Hospital, 3rd Edn. Edited by L. Firestone, P. W. Lebowitz and C. E. Cook. Published (1988) by Little, Brown and Co. Pp. 728; indexed; illustrated. Price £13.95.

In October 1846, Morton gave the first public demonstration of ether anaesthesia in the Massachusetts General Hospital, and placed the location firmly upon the anaesthetic map of the world. This little book continues to mark its position.

This 3rd edition of "Lebowitz" has a new senior editor and some 34 contributors. The chapters have been arranged in three sections. The largest, Administration of General Anaesthesia, occupying some 70% of the text, lies between two sections of equal size: Evaluation of the Patient, and Patient Care in Other Settings. A comprehensively constructed drug appendix follows. This format is explained by the editors' stated intention to produce an accessible form of accurate, practical knowledge. It is up to date, incorporating for example, the Harvard standards for minimal monitoring.

The North American influence is pervasive—from emphasis on preoperative explanation of risks to the patient, through advocacy of closed circle anaesthesia, to the exclusive use of US drug names. As an example of this exclusivity, the reviewer is disappointed to find no mention of Ayre's T piece. However, the book is more comprehensive than its British equivalents, which tend to concentrate upon emergency anaesthesia.

The first section covers evaluation of the patient. A problem encountered frequently by junior anaesthetists is that of medical disease complicating anaesthesia, and this section has some notable omissions—neurological and haematological diseases, for example. The second section covers administration of anaesthesia. Here are examples of institutional practice, for example the use of 100% nitrous oxide in the early stages of closed circle anaesthesia. Much space is devoted to the intricacies of the copper kettle vaporizer; the section on positioning the patient is dismissed rather briefly, and the omission of a description of a retrograde catheter technique for difficult tracheal intubation is notable. The chapter on obstetric anaesthesia omits any reference to Mendelson's syndrome. However, there is an excellent chapter on neuromuscular blockade and monitoring, a good account of local anaesthetic drugs (with the notable omission of prilocaine), which would be useful reading for any medical student, and a succinct account of regional techniques.

The final section contains a short chapter on resuscitation which includes neonatal resuscitation. The chapter on respiratory intensive care contains much valuable information.

This is a useful little book which fulfils its aim as a handbook by fitting, albeit heavily, into a coat pocket. As a method of data retrieval it relies heavily upon familiarity with the text rather than the index, which is by no means comprehensive. The text is illustrated, but only sparsely as befits the format of a synopsis; it is not clear what merits the choice of illustrations. The typeface has been changed from that of the previous edition and there is less space between headings, resulting in a less readable text.

The new Senior House Officer may find this book heavy going, but the more experienced SHO or registrar seeking a succinct source of reference will find much of value here; the chapters are short and useful as a revision text, but the format will not suit all readers. However, now that *Synopsis* has been removed from the white coat pocket and, by virtue of its size, been placed on the library shelf, for some individuals this text may be a suitable successor.

D. Fell

Papers for publication and all editorial communications should be addressed to the Editor, University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW; business communications to the publishers: Professional & Scientific Publications Ltd, BMA House, Tavistock Square, London WC1H 9JR.

The GUIDE TO CONTRIBUTORS can be found on pages viii, x & xii of the advertisement section of this issue.

Published monthly: Annual subscriptions: UK/Eire £54.00; Abroad £85.00; USA $117.00 (direct orders only). Trainee rate UK/Eire £33.00; Abroad £50.00. Airmail rates on application. ISSN 0007-0912. Orders must be accompanied by payment; cheques should be made payable to Professional and Scientific Publications. Orders and payments should be sent to Professional and Scientific Publications, BMA House, Tavistock Square, London, WC1H 9JR. Orders in the United States of America may be sent to Professional and Scientific Publications, Box 560B, Kennebunkport, Maine 04046.

Group Advertisement Manager, Mr R. Hayzen.
Advertisement Manager, Mrs S. Rowe
BMA House, Tavistock Square, London WC1H 9JR. 01-387 4499.

Whilst every effort is made by the publishers and editorial committee to see that no inaccurate or misleading data, opinion or statement appears in this Journal, they wish to make it clear that the data and opinions appearing in the articles and advertisements herein are the responsibility of the contributor or advertiser concerned. Accordingly, the publishers and the editorial committee and their respective employees, officers and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinion or statement. Whilst every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described within this Journal, should only be followed in conjunction with the drug manufacturer's own published literature

---

© Copyright: 1988 British Journal of Anaesthesia
All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the *British Journal of Anaesthesia*.

Published by Professional and Scientific Publications.
Printed in Great Britain by the University Press, Cambridge

The latest Keynes Press publication marks the ninetieth anniversary of a major breakthrough in tropical medicine

This day designing God
  Hath put into my hand
A wondrous thing. And God
  Be praised. At His command,

I have found thy secret deeds
  Oh million-murdering Death.

I know that this little thing
  A million men will save—
Oh death where is thy sting?
  Thy victory oh grave?

Not many scientists are moved to verse by the fruits of their research, but few results are s momentous as the one celebrated by Ronald Ross in *The Great Malaria Problem and its Solution.* Adapted from Ross's memoirs, this Keynes Press edition gives the full story of Ross's discovery of the mode of transmission of malaria by the Anopheles mosquito. Engagingly written, it is the frank and accurate picture of four years' painstaking work, full of hope, despair, elation, frustration, and what Ross describes as the "sacred passion for discovery." It also hows the close and moving scientific partnership between Ross and Patrick Manson, the "father of tropical medicine", as evidenced in the 155 letters exchanged between them over this period.

Fully illustrated, and with an introduction by L J Bruce-Chwatt, emeritus professor of ropical public health at the University of London, this unique volume provides a fascinating insight into the process of scientific research as well as a self portrait of one of the most impressive and colourful individuals in the history of tropical medicine.

PLATE VII

(From a Mauritian Newspaper, 1908.)

THE KEYNES PRESS

The Keynes Press
Limited editions of medical classics,
handsomely printed and bound.

Price: Inland £45.00; Abroad £52.00;
USA $73.00, including postage.

Order from:
British Medical Journal (Keynes Press)
PO Box 295, London WC1H 9TE

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 61, No. 2 *Published monthly* AUGUST 1988
Annual subscriptions (post free): U.K./Eire £54.00; Abroad £85.00; USA $117.00 (Direct orders only); Trainee rate: U.K./Eire £33.00; Abroad £50.00. Airmail rates on application ISSN 0007-0912

Subscription Department, Professional and Scientific Publications, BMA House, Tavistock Square, London, WC1H 9JR, England

---

CONTENTS

PAGE

EDITORIAL: Test doses in extradural block........ 129
D. B. Scott

ORIGINAL ARTICLES

Influence of premedication on lignocaine-induced toxicity and plasma concentrations of lignocaine . 131
J. Haasio, R. Hekali and P. H. Rosenberg

Effect of dextrose concentration on the intrathecal spread of amethocaine........................ 135
A. Lee, D. Ray, D. G. Littlewood and J. A. W. Wildsmith

Effects of posture and baricity on spinal anaesthesia with 0.5% bupivacaine 5 ml. *A Double-Blind Study*.. 139
R. W. D. Mitchell, G. M. R. Bowler, D. B. Scott and H. H. Edström

Spinal anaesthesia with hyperbaric bupivacaine: effects of concentration and volume when administered in the sitting position.................. 144
R. P. Alston, D. G. Littlewood, R. Meek and H. H. Edström

Extradural bupivacaine or lignocaine anaesthesia for elective Caesarean section: the role of maternal posture.. 149
J. A. Reid and J. Thorburn

Buffering capacity of normal and inflamed tissues following the injection of local anaesthetic solutions.. 154
A. Punnia-Moorthy

Effect of patient-controlled analgesia on plasma catecholamine, cortisol and glucose concentrations after cholecystectomy.......................... 160
I. W. Møller, K. Dinesen, S. Søndergård, U. Knigge and H. Kehlet

No effect of continuous i.p. infusion of bupivacaine on postoperative analgesia, pulmonary function and the stress response to surgery.............. 165
N. B. Scott, T. Mogensen, A. Greulich, N. C. Hjortsø and H. Kehlet

Intercostal nerve blockade producing analgesia after appendicectomy.............................. 169
P. Bunting and J. F. McGeachie

Pharmacodynamics of alfentanil as a supplement to nitrous oxide anaesthesia in the elderly patient... 173
H. J. M. Lemmens, A. G. L. Burm, J. G. Bovill and P. J. Hennis

Comparison of large dose of vecuronium with pancuronium for long-lasting neuromuscular blockade 180
K. Rørvik, P. Husby, L. Gramstad, J. S. Vamnes, L. Bitsch-Larsen and M. E. Koller

Central and regional haemodynamics during controlled hypotension produced by adenosine, sodium nitroprusside and nitroglycerine. *Studies in the Pig*.. 186
N. Norlén

Haemodynamic and heart rate reflex responses to propofol in the rabbit. *Comparison with Althesin* . 194
D. W. Blake, B. Jover and B. P. McGrath

Effects of inhalation anaesthetics on filtration of venous gas emboli by the pulmonary vasculature. 200
J. Katz, B. C. Leiman and B. D. Butler

Ketamine fails to protect against ischaemic neuronal necrosis in the rat.......................... 206
M. L. Jensen and R. N. Auer

Predicting difficult intubation...................... 211
M. E. Wilson, D. Spiegelhalter, J. A. Robertson and P. Lesser

Learning fibreoptic intubation: use of simulators *v.* traditional teaching.......................... 217
A. Ovassapian, S. J. Yelich, M. H. M. Dykes and M. E. Golman

The morphine hydrogel suppository. *A New Sustained Release Rectal Preparation*................ 221
C. D. Hanning, A. P. Vickers, G. Smith, N. B. Graham and M. E. McNeil

RAPID COMMUNICATIONS

Absorption and bioavailability of nebulized morphine... 228
J. Chrubasik, H. Wüst, G. Friedrich and E. Geller

The incidence of sinusitis in patients with nasotracheal intubation............................ 231
M. Hansen, M. R. Poulsen, D. K. Bendixen and F. Hartmann-Andersen

CASE REPORT

Prolonged suxamethonium-induced neuromuscular blockade associated with organophosphate poisoning.. 233
F. Pérez Guillermo, C. M. Martinez Pretel, F. Tarín Royo, M. J. Peña Macias, R. Alvarez Ossorio, J. A. Alvárez Gómez and C. J. Vidal

CORRESPONDENCE

Components of anaesthesia........................ 237
Suxamethonium myalgia.......................... 238
Assessment of the Datex Relaxograph in accessory nerve stimulation.............................. 238
Rapid sequence induction in pregnancy-associated hypertension—the role of magnesium........... 239
Long term use of the Vocalaid tracheostomy tube for tracheal toilet................................ 240
Bradycardia following vecuronium................ 240
Transfer from recovery room to ward............. 241
Fresh gas flow requirements with the ADE anaesthetic system................................. 241

BOOK REVIEWS

Current European Anaesthesiology................ 243
Aspects of Recovery from Anaesthesia............. 243
Databook of Anaesthesia and Critical Care Medicine. 243
Shock and the Adult Respiratory Distress Syndrome . 244
Postoperative Pain Control........................ 244
Recovery Room Care............................. 244
Clinical Anesthesia Procedures of the Massachusetts General Hospital.......................... 245